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# THE GENETIC MECHANISM OF GALACTOSAEMIA*

BY

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(RECEIVED FOR PUBLICATION OCTOBER 8, 1959)

Galactosaemia is a heredity disease of carbohydrate metabolism characterized by a failure to thrive, vomiting and jaundice in early infancy. Babies with this condition usually present with these symptoms and they are found to have enlarged firm livers, which soon become cirrhotic; this has been borne out by autopsy reports. They may be oedematous and have a tendency to bleed easily. Cataracts and mental retardation are common complications. The diagnosis can be confirmed by a markedly elevated galactose tolerance test and the finding of galactose in the urine. Schwarz, Golberg, Komrower and Holzel (1956) showed that galactose-1-phosphate accumulated in the erythrocytes of galactosaemic children if they were given galactose or milk. This indicated that galactokinase, which is the enzyme that converts galactose to galactose-1-phosphate, must be present in such individuals. In the same year, Isselbacher, Anderson, Kurahashi and Kalckar (1956) demonstrated a deficiency of galactose-1-phosphate uridyl transferase in the red blood cells of these children. This indicated that the site of the metabolic block in galactosaemia was at the step of:

$$\text{Galactose-1-PO}_4 + \text{UDP glucose} \rightleftharpoons \text{UDP galactose} + \text{glucose-1-PO}_4.$$

It is now generally agreed that galactosaemia is transmitted by a Mendelian autosomal recessive gene. This is because of its frequent occurrence amongst siblings, its equal distribution in both sexes and the increased incidence of consanguineous matings amongst the parents of these children. Holzel and Komrower (1955) attempted to study the genetics of this condition by subjecting the parents of galactosaemic children to a galactose tolerance test. In only one family were they able to show that both parents were abnormal. In each of the four other families tested only one of the parents gave an abnormal result; Durand and Semach (1955) found an abnormal galactose tolerance test in one parent; Bray, Isaac and Watkins (1952); Bain, Bowden, Chute, Jackson, Sass-Kortsak and Walker (1957); Schreier, Acker and Henckel (1957); and Bennett (1958) failed to demonstrate any abnormalities in the parents they tested. Hsia, Huang and Driscoll (1958) have since shown that a group of heterozygotes can be detected by estimating the blood level of galactose-1-phosphate uridyl transferase. This is discussed in more detail later.

The purpose of this paper is to present a complete family with galactosaemia and to give evidence that the disease is transmitted by a Mendelian autosomal recessive gene; it also sets out to show how enzyme studies in this family confirm the recessive mode of inheritance, that heterozygotes as a group can be detected and finally it demonstrates that galactosaemia can be present in a relatively unaffected adult.

### Clinical Description of Family J

This family came to our notice from a genetic point of view as a family suffering from renal glycosuria. On investigation it was found that the reducing substance in the urine was galactose and as a result, all available members of the family have been studied. The pedigree is given in Fig. 1 and clinical details below:

$I_1$ R.W., born 1894, had been thought to have diabetes mellitus for 16 years but has never needed insulin. The reducing substance in his urine has recently been shown to be galactose. Now he is in reasonably good health attending to his office business daily, and he is of above average intelligence. His eyesight is impaired because of cataracts and also he has an enlarged firm liver.

$I_2$ B.W., born 1900, is healthy and has no reducing substance in her urine.

$II_1$ R.W., born 1925, was known to have had a reducing substance in his urine since the age of 11 and to have a normal glucose tolerance test. He was healthy but not robust, and when put on an ulcer regime containing one or two pints of milk a day he found

* These studies were aided by grants from the Chicago Community Trust and the Otho S.A. Sprague Memorial Institute.

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that he felt quite ill and so stopped it himself. He has five children, all of whom are well.

$II_2$ A.J., born 1926, had been thought to have renal glycosuria for the past 10 years and when the diagnosis had been established in her children, it was found that the reducing substance in her urine was also galactose. She prefers to avoid milk, and has had much less intermittent diarrhoea, fewer headaches and has felt generally in better health since being on a milk-free diet.

$II_3$ K.M., born 1928, has remained in reasonable health but had a reducing substance in her urine when she was pregnant. She has had one miscarriage and two healthy children.

$II_4$ W.W., born 1931, was discharged from the services because a reducing substance was persistently found in his urine. Otherwise he was healthy.

$II_5$ H.F., born 1935, has never been robust; she looks unwell with a rather pale translucent skin. She has had five pregnancies; two ended in miscarriages, two were premature births, the babies dying, and one a healthy child. She felt ill when pregnant, and was known to have a reducing substance in the urine at those times.

$II_6$ S.C., born 1937, was in good health and has no reducing substance in her urine.

$II_{11}$ J.J., born in 1920, admitted to no ill health and came from a large healthy family.

$III_1$ T.J., born in 1948 at term by caesarean section because of a transverse lie, weighed 6 lb. 14½ oz. Although not particularly jaundiced at birth, he was an extremely difficult baby to feed because of vomiting. None of the usual artificial feeds suited him. In spite of his not regaining his birth weight until he was 1 month old, he was always an active baby. He smiled at 5 weeks, had some control of his head at 8 weeks, sat in a high chair at 5 months, pulled himself up to stand at 6 months, walked with support at 11 months and by himself at 1 year. He could say single words at 15 months and talked at 22 months. Hence, there has been no evidence of any mental retardation and his subsequent progress at school has always been more than satisfactory. At about the age of 9 months, his mother took him off regular milk because she felt it did not suit him, and his condition subsequently improved. Since the age of about 1 year, he has complained of headaches and his mother correlated these with the taking of milk. He has had many unpleasant ill-defined episodes, which culminated in an alarming attack, in which he shook violently, had blurred vision, profuse sweating and almost lost consciousness. This attack had occurred after gulping a large bowl of milk and cereal at breakfast and was relieved by taking a sugar drink. At this time he was known to have a reducing substance in his urine with a normal glucose tolerance curve. It was the investigation of this presumed hypoglycaemic attack that lead to the establishment of the diagnosis of galactosaemia. Examination now revealed him to be a tall, thin boy, of 9 years old, weight 65 lb., height 55 in. He has red hair and a rather translucent skin, bilateral cataracts and pale retinae; the liver and spleen were not palpable, and there were no other abnormal physical findings. The reducing substance in his urine was shown to be galactose by its failure to ferment with yeast; this was confirmed by the osazone test. Other laboratory data are given in Table 1. Since being on a milk-free diet, he has grown 1 in. and gained 3½ lb. in six months. He has been free of headaches, has felt much better and, instead of being a rather docile apprehensive boy, he has more energy and is full of spirit; in addition, his scholastic attainments have improved. Any relaxation of his diet, however, brought back the headaches and symptoms reminiscent of the hypoglycaemic attack.

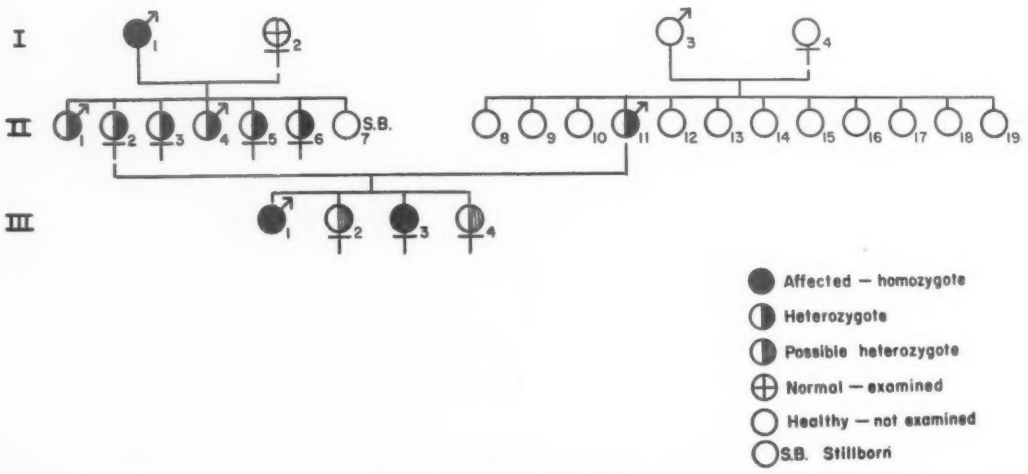


FIG. 1.—Pedigree on Family J.

TABLE 1

LABORATORY AND BRIEF CLINICAL DATA ON FAMILY J

| | | Gal-1-P Uridyl Transferase Level (units/g. Hb) | | | | Galactose Level (mg./100 ml. blood) | | | Cataracts | I.Q. | Probable Genetic Status |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Mean | S.D. | Range | | No value should be more than 50; reading should return to fasting level in 2 hrs | | | | | |
| Values for Normals .. | | 4·13 | ±1·4 | 2·8–7·0 (16)* | | | | | | | |
| Values for Heterozygotes | | 2·9 | ±1·1 | 1·1–5·5 (23)* | | Usually normal | | | | | |
| Values for Affected .. | | 0·6 | ±0·47 | 0 –1·1 (16)* | | Values more than 50 mg. | | | | | |
| *PEDIGREE* Ref. No. | Initials | Random | Fasting | 1 hr | 2 hrs | Fasting | 1 hr | 2 hrs | | | |
| I 1 | R.W. | | 0·9 | | | 59 | 115 | 42 | + | N | Homozygote |
| I 2 | B.W. | 3·4 | | | | | | | | N | Unaffected |
| II 2 | A.J. | | 1·7 | 1·8 | 1·7 | 8 | 28 | 6 | | N | Heterozygote |
| II 11 | J.J. | | 1·8 | 1·0 | 0·9 | 7 | 31 | 10 | | N | Heterozygote |
| III 1 | T.J. | | 0·6 | 0·6 | 0·4 | 7 | 86 | 54 | + | N | Homozygote |
| III 2 | M.J. | | 1·8 | 2·0 | 2·0 | 11 | 49 | 4 | | N | Possible heterozygote |
| III 3 | S.J. | | 1·0 | 0·8 | 0·5 | 10 | 45 | 10 | + | N | Homozygote |
| III 4 | B.J. | | 2·5 | 2·4 | — | 10 | 83 | — | | N | Possible heterozygote |
| II 1 | R.W. | 1·1 | | | | | | | | | Heterozygote |
| II 3 | K.M. | 3·4 | | | | | | | | | Heterozygote |
| II 4 | W.W. | 2·1 | | | | | | | | | Heterozygote |
| II 5 | H.F. | 2·5 | | | | | | | | | Heterozygote |
| II 6 | S.C. | 4·1 | | | | | | | | | Heterozygote |

* Number of cases of which mean is recorded.

$III_2$ M.J. was born in 1950. Although her mother had some hypoglycaemic episodes during this pregnancy, she was born at term by caesarean section weighing 7 lb. 9 oz. She was breast fed for four months, thrived well from the beginning and has always been healthy, although she had an intussusception at the age of 4 months. She passed her milestones normally and is now a healthy intelligent girl.

$III_3$ S.J., born 1953, at term by caesarean section, weighing 6 lb. 14 oz. Vomited constantly from birth and had intermittent diarrhoea. When mother's milk failed she was extremely difficult to feed on cow's milk. When first admitted to the hospital at 3 months with a tentative diagnosis of congenital hypertrophic pyloric stenosis she weighed only 8 lb. Every type of milk feed was tried, but all were vomited. At 7 months of age she had a convulsion, which was thought to be related to an attack of pyelitis; at this time she only weighed 10 lb. She passed her milestones normally, sat at 6 months, walked between 10 and 11 months and was talking at the age of 2 years. She had frequent headaches, a poor appetite and 'chills' after drinking milk.

On examination she was found to be 39½ in. tall and weighed 28 lb. She, too, has red hair and a pale translucent skin unlike her two unaffected siblings. She had a palpable liver and bilateral cataracts but was otherwise normal. When the diagnosis was established in her brother T.J., her mother realized that she too was suffering from the same disease and enzyme studies confirmed this. Since then she has been on a milk-free diet, has grown 1¼ in. and gained 5 lb. in six months. She has been free of headaches, felt better and done better in school though perhaps not quite so dramatically as her brother. Neither T.J. nor S.J. can tolerate more than 1 oz. of milk on alternate days without the recurrence of symptoms.

$III_4$ B.J. was born in 1955, three weeks prematurely, by caesarean section because of a transverse lie. She weighed 7 lb. 11 oz. at birth and has thrived ever since. There were no feeding difficulties but a congenitally dislocated hip was diagnosed when she was 4 months old. It has been satisfactorily treated with splints and she stood at 7 months, walked at 13 months and is now a bright alert little girl.

### Laboratory Data

**Methods and Results.** Galactose tolerance tests were done in the usual manner after an overnight fast. *D*-galactose was given orally in doses of 40 g. for adults, 1·25 g./kg. body weight for children and 1·75 g./kg. body weight for infants. A fasting blood sample, and others, one and two hours after taking the galactose, were collected in heparinized tubes and packed in ice until they were brought to the laboratory, the same samples being used both for the galactose determinations and the enzyme assays.

Blood galactose was determined by removing the glucose with glucose oxidase and estimating the remaining reducing substances by the Nelson Somogyi method.

Galactose-1-phosphate uridyl transferase was estimated by the method originally described by Anderson, Kalckar, Kurahashi and Isselbacher (1957). The method depends upon incubating a haemolysate of the red cells which contain the enzyme with known amounts of galactose-1-phosphate and uridine diphosphoglucose (UDPG). The reaction then proceeds from left to right as shown by the equation above. A unit of enzyme is that amount which will convert one micromole of UDPG to UDPGalactose in an hour. After the incubation period the remaining UDPG is estimated by means of uridine diphosphoglucose dehydrogenase in

TABLE 2
DETAILS ON PUBLISHED CASES OF GALACTOSAEMIA

| Author | Case No. | Details of Families |
|---|---|---|
| Von Reuss (1908) | | ● |
| Goppert (1917) | | ♂♂♂● |
| Fanconi (1933) | + | ○○○♀♀○○○○○● |
| Boer (1932) | | ●● order not stated |
| Mason and Turner (1935) | | ♀♂♀♀♀●○ |
| Norman and Fashena (1943) | | ○● |
| Mellinkoff, Roth and MacLaggan (1945) | | ● |
| Bruck and Rapoport (1945) | | ● |
| Goldbloom and Brickman (1946) | 1 | ○● |
| | 2 | ● |
| Goldstein and Ennis (1948) | | ○○● order not stated |
| Greenman and Rathbun (1948) | | ● |
| Bell, Blair, Lindsay and Watson (1950) | | ♀● |
| Donnell and Lann (1951) | 1 | ● |
| | 2 | ◇♂♀● |
| DuShane and Hartmann (1951) | | ○○○○● |
| Townsend, Mason and Strong (1951) | 1 | ○● |
| | 2 | ◇●●♀ |
| | 3 | ○○● |
| | 4 | ● |
| Ellenburg and Peterson (1951) | | ♀♀♂● |
| Gorter (1951) | 1 | ○○♀● |
| | 2 | ● |
| McCue (1951) | | ● |
| De Haas (1951) | | ○○○○○○○●● |
| Enns (1951) | | ● |
| Falls, Lowrey and Anderson (1951) | | ● |
| Edmonds, Hennigar and Crooks (1952) | | ●○○○○○○○ |
| Langewisch and Bigler (1952) | | ● |
| Bray, Isaac and Watkins (1952) | 1 | ● |
| | 2 | ● |
| | 3 | ◇● |
| Brodie, J. L. (1952) | | ●⊕⊕●●● |
| (1958) | | As Brodie (1952) |
| Pitt (1952) | | ● |
| Reiter and Lasky (1952) | | ● |
| Johns (1953) | | ♂♂● |
| Hsia (unpublished data) (1952) | 1 | ●♂● |
| | 2 | ♀● |
| | 3 | ● |
| Maris and Valcke (1953) | | ♂● |
| Birdsong and Wood (1953) | | ○○● |
| Hartmann, Grunwaldt and James (1953) | | ● |
| Johnson (1953) | 1 | ○○○♀◇○● |
| | 2 | ♀♂● |
| | 3 | ● |
| Patz (1953) | 1 | ◑◑● |
| | 2 | ● |
| Fox, Fyfe and Mollison (1954) | | ♂● |
| LoPresti, Itani and Rice (1952) | | ♀●● |
| Lockhart and Roboz (1954) | | As LoPresti *et al.* (1952) |
| Bickel and Thursby-Pelham (1954) | | ◔● |
| Hudson *et al.* (1954) | 1 | ○○●♀ |
| | 2 | ♀♂●♂● |
| | 3 | ○● |
| Arthurton and Meade (1954) | | ○●○○○ |
| Cox and Pugh (1954) | 1 | ◇●♂♀●◇ |
| | 2 | ♀♀● |
| | 3 | ○○● |
| Hartmann, McCoy, Swarm and Nakasato (1954) | | ● |
| Lodding (1954) | + | ● |
| Jeune, Charrat and Loaec (1954) | | ♂♂♀♂♀♂● |
| Holzel and Komrower (1955) | 1 | ⊕●● |
| | 2 | ● |
| | 3 | ●●♀♂ |
| | 4 | ♂● |
| | 5 + | ●⊕●⊕ |
| Clay and Potter (1955) | | ● |
| Mortensen and Sondergaard (1955) | | ● |
| Ritter and Cannon (1955) | | ● |
| Durand and Semach (1955) | | ♂●● |
| Rathbun (1955) | | ● |
| Flury and Berger (1955) | + | ♀♀● |
| Haas and Newman (1955) | | ● |
| Salt, Ross and Gerrard (1955) | | ● |
| Smith (1955) | | ◑♂♂◇● |
| Kalckar, Anderson and Isselbacher (1956) | 1 | ♀●●● |
| | 2 | ● |
| | 3 | ♂● |
| Komrower, Schwarz, Holzel and Golberg (1956) | 1 | ◇◇◇◔⊕● |
| | 2 | ● |
| Turnbull (1956) | | ◔○● |
| Clément, Combes-Hamelle and Saada (1956) | | ○○○●○○○ order not stated |
| Rodier (1957) | | ● |
| Gillot, Schaeffer and Dalaut (1957) | | ● |
| Bain, Bowden, Chute, Jackson, Sass-Kortsak and Walker (1957) | 1 | ● |
| | 2 | ♂♂● |
| | 3 | ●● |
| | 4 | ●♂♀● |
| | 5 | ◇◇●● |

TABLE 2 (*continued*)

| Author | Case No. | Details of Families |
|---|---|---|
| Schultze-Jena and Schafer (1957) | 1 | ◇ ♂ ♂ ♂ |
| | 2 | ○ ○ ◑ ◑ ♂ |
| Schreier, Acker and Henckel (1957) | | ○ ○ ♀ |
| Wilhelm (1957) | | ♂ |
| Bennett (1958) | | ○ ♂ |

KEY

| | |
|---|---|
| Male | ♂ |
| Female | ♀ |
| Sex not recorded | ○ |
| Miscarriage or stillbirth | ◇ |
| Cataracts | ◐ |
| Cirrhosis | ◕ |
| Reducing substance in urine | ◔ |
| Trace of reducing substance in urine | ◔ |
| Abnormal galactose tolerance test | ⊕ |
| Galactosaemia | ● |
| Consanguinity | + |

the presence of DPN. The amount of haemoglobin in the haemolysate is calculated and the enzyme expressed as units per g. of Hb. Huang, Hugh-Jones and Hsia (1959) have described these methods in detail.

Using these methods the results obtained in this family are given in Table 1. Normal values for this laboratory are given at the top of the Table. The grandfather, who clinically had had a reducing substance in his urine for years (recently proven to be galactose), a large liver and cataracts, was found to have an abnormal galactose tolerance test and an enzyme level within the affected range. The two of his grandchildren, who had typical histories of galactosaemia, also had enzyme levels within the affected range. The enzyme determinations on the grandfather's six children showed them, as a group, to be heterozygotes and the only one who was free of symptoms had the highest enzyme level.

### Genetic Analysis of Literature

All the available published literature on galactosaemia has been reviewed. All families containing a case of galactosaemia have been tabulated (Table 2). For a case to be accepted as one of galactosaemia it must have had the typical clinical history of failure to thrive and feeding difficulties since birth, jaundice and an enlarged liver, a reducing substance in the urine after the first week of life and albuminuria. The reducing substance must have been proven to be galactose either by (1) its failure to ferment with yeast, (2) positive mucic acid test, (3) osazone crystal formation or (4) by paper chromatography. Many cases also had cataracts, were oedematous in the first week of life and had a tendency to bleed. Once a case had been diagnosed in a family others were quite often diagnosed retrospectively. These have been accepted provided they had three of the four following findings: typical history, cirrhosis, a reducing substance in the urine and cataracts. Using these criteria all the families, except those containing only one child, have been tabulated in Table 3.

Clinically, as had already been mentioned, it seems likely that galactosaemia is transmitted as a recessive gene. To confirm this the family data collected from the literature have been analysed

TABLE 3

ANALYSIS OF THE 57 SIBSHIPS WITH ONE OR MORE CASES OF GALACTOSAEMIA, COLLECTED FROM THE LITERATURE, BY THE *A PRIORI* METHOD (ONE CHILD FAMILIES OMITTED)

| Family Size | No. of Families | Observed No. of Cases | | | | Expected No. of Cases | Variance |
|---|---|---|---|---|---|---|---|
| | | Male | Female | Not Stated | Total | | |
| 2 | 15 | 9 | 6 | 5 | 20 | 17·142 | 1·83 |
| 3 | 20 | 16 | 13 | 3 | 32 | 25·946 | 5·26 |
| 4 | 10 | 12 | 4 | 2 | 18 | 14·628 | 4·20 |
| 5 | 4 | 5 | 1 | — | 6 | 6·556 | 2·37 |
| 6 | 2 | 2 | 3 | — | 5 | 3·650 | 1·55 |
| 7 | 4 | 3 | 1 | — | 4 | 8·078 | 3·88 |
| 9 | 1 | — | — | 2 | 2 | 2·433 | 1·38 |
| 11 | 1 | 1 | — | — | 1 | 2·871 | 1·805 |
| | 57 | 48 | 28 | 12 | 88 | 81·304 | 22·275 |

Standard deviation = 4·72
Observed cases, excluding cases from families of size one = 88
Expected number of cases = 81

$$\text{'t'} = \frac{\text{difference between the observed and expected number of cases}}{\text{standard deviation}} = \frac{7}{4{\cdot}72} = 1{\cdot}5$$

7 degrees of freedom
$p > 0{\cdot}05$

by two methods. In each instance it has been shown that the observed frequency of cases was not significantly different from the theoretical incidence calculated for a recessive mode of inheritance.

In the first instance the data was analysed using the Weinberg sib method (Schultz, 1936). The formula for a recessive mode of transmission is:

$$\frac{Ta-P}{T-P} \text{ Should equal } 0{\cdot}25$$

$$SE = \sqrt{\frac{pq}{T-P}}$$

Where: Ta = Total affected children in all the families
T = Total children in all the families
P = Probands
p = Expected frequency of affected
q = Expected frequency of remainder

There were 36 families with only one child, of which 18 were males, 12 females and in six the sex was unrecorded; when these were added to the data from Table 3, the formula became:

$$\frac{124-93}{246-93} = 0{\cdot}2 \qquad SE = \frac{0{\cdot}25 \times 0{\cdot}75}{153} = 0{\cdot}035$$

Thus, the difference between the observed and expected value was not significant.

The data were also analysed by the '*a priori*' or Apert's method. Calculating the expected number of children to be affected from Hogben's tables reproduced by Neel and Schull (1954) it will be seen from Table 3 that in these 57 families (families with only one child were omitted in these calculations) there should have been 81·3 affected children. The number observed was 88 The standard deviation is the square root of the sum of the variances. The difference between the observed and expected was 7; this divided by the standard deviation gave a 't' value of 1·5 which for 7 degrees of freedom was not significant. Therefore, the difference between the observed and expected number of affected children was again not significant.

In the total series, where the sex had been recorded, there were 66 males to 40 females. From Table 2 the sex of the unaffected siblings, where recorded, gave a ratio of 32 males to 25 females. There was obviously no significant difference between these two figures. Many of these galactosaemic children had died within the first month of life; therefore, as another comparison, the sex ratio at birth of the large Birmingham series reported by Crosse (1949) has been used. In this series of over 19,000 births there were 53% males and 47% females. This gave a calculated incidence of 56 males to 50 females for this series. Using the $\chi^2$ test between the observed and calculated values t = 1·92; 1 d.f.; $p > 0{\cdot}05$. So there was no statistical evidence to suggest that this difference in sex incidence was of significance. These statistical analyses confirm the clinical impression that galactosaemia is transmitted by a Mendelian autosomal recessive gene.

## Discussion

As has already been mentioned, attempts to detect the heterozygous carriers of this condition by stressing them with galactose tolerance tests have not been sufficiently precise to be successful.

During the past year three groups of workers have been able to demonstrate an abnormality amongst the heterozygous carriers of galactosaemia. Originally Hsia *et al.* (1958) reported a reduction of the enzyme galactose-1-phosphate uridyl transferase in the red cells of a group of 12 heterozygotes as compared with 11 normal controls. Bretthauer, Hansen, Donnell and Bergren (1959) modified the original method of assaying the enzyme and found that they were able to detect the heterozygous group with less overlap of the results between carriers and controls than the previous worker. Kirkman and colleagues (Kirkman and Kalckar, 1958; Kirkman and Bynum, 1959), have reported a more refined technique of enzyme assay using oxygen consumption and by this method have also shown a decrease of enzymatic activity amongst the relatives of galactosaemic individuals. The first study has been enlarged upon by the addition of further data, and also by a second attempt to detect the carrier state by measuring the accumulation of hexose-1-phosphate in the red cells under the stress of a galactose tolerance test (Huang *et al.*, 1959). The results of these enzyme assays have been analysed and are included at the top of Table 1. Although it may be difficult to evaluate the significance of the results from an individual, the difference between the enzyme levels of the normal group and the heterozygous carriers gave a value for 't' of 3·0 with 37 degrees of freedom (16 normal controls and a group of heterozygotes consisting of 18 parents and five offspring of galactosaemic patients). This difference was highly significant ($p < 0{\cdot}005$). That the value for heterozygotes with one abnormal gene fell between the normals with no abnormal genes and the homozygotes with two abnormal genes lent further support to the recessive mode of transmission.

The interest in this family lay in the chance discovery of an affected adult who had affected grandchildren. From our genetic analysis of the literature we would have expected him to have two abnormal genes for galactosaemia and therefore, for him to have handed on one of the abnormal genes to each of his children. This has been elegantly confirmed by doing the enzyme levels in this family; the average enzyme level for his six children was 2·5, which was well within the heterozygous range. That one of his daughters should have married another unrelated heterozygous carrier for galactosaemia was a chance of fate, but of great academic interest. That the father of these grandchildren was a heterozygote was confirmed by the

enzyme studies. Therefore, in this family study, there was a clear confirmation of the recessive mode of inheritance and a demonstration of the laboratory techniques for detecting heterozygotes. In addition, the use of enzyme determinations was shown in confirming the clinical diagnosis.

It was not generally known that a person with galactosaemia could live to be an adult in reasonable health without treatment. One other adult case has been found by this laboratory. There were three cases in the literature reported by Ritter and Cannon (1955) and by Durand and Semach (1955), who were not diagnosed until the ages of 5, 14 and 8 years respectively. They showed little ill effects other than cataracts and no doubt could have lived normally with no more serious effects than had the grandfather $I_1$ R.W. Presumably his two grandchildren who were not diagnosed until the ages of 9 and 5 years could also have survived. Mason and Turner's (1935) original case is now in his late 20's but he is severely retarded.

Another unusual feature in this family was the symptomatology among the heterozygotes. $II_{1\text{-}6}$ were all heterozygotes because their father $I_1$ was a homozygote. This has been confirmed by the enzyme studies. Three of his four daughters felt unwell when pregnant and had mellituria; in one $II_2$, this has been proven to be galactose. His two sons had mellituria and after reducing their intake of milk their conditions improved. The only child in this family who did not have symptoms had an enzyme level at the upper end of the heterozygous range. Ellenburg and Peterson (1951) and Hudson, Ireland, Ockenden and White-Jones (1954) have reported siblings of affected cases who showed a trace of reducing substance in the urine. LoPresti, Itani and Rice (1952) and Kalckar, Anderson and Isselbacher (1956) each record a paternal grandfather who was intolerant of milk; Holzel and Komrower (1955) state that one of the fathers of their patients became ill after taking 30 g. of galactose daily. Abnormal galactose tolerance tests have been demonstrated in some parents and siblings though not regularly (Brodie, 1952; Holzel and Komrower, 1955; Durand and Semach, 1955; Komrower, Schwarz, Holzel and Golberg, 1956). This was not surprising once it was realized that the heterozygote has less enzyme available than normal and in some cases this was nearly as little as in affected individuals.

## Summary

A family is presented in which the grandfather was proven to have galactosaemia by galactose tolerance tests and by the determination of the enzyme galactose-1-phosphate uridyl transferase level in his blood. His six children were shown by similar enzyme studies to be heterozygous carriers of the condition and one of these married another unrelated heterozygous carrier and they had two affected children in their family of four. A complete review of the literature is given and genetic analysis of the data collected strongly suggests that galactosaemia is transmitted as a Mendelian autosomal recessive gene. The results of our laboratory studies in the detection of the heterozygous carrier in galactosaemia are given and these confirm, in this family, this mode of transmission.

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# THE OXYGEN TENSION OF THE BLOOD IN THE UMBILICAL CORD AND THE INTERVILLOUS SPACE

BY

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During recent years there has been a revival of the interest in oxygen saturation in the umbilical blood; this work was started in the 1930's by Haselhorst and Stromberger (1931) and several papers have been published by different groups (Walker and Turnbull, 1953; MacKinney, Ehrlich, Goldberg and Cantwell, 1955; Rooth and Sjöstedt, 1955, 1957; Bancroft-Livingston and Neill, 1957; Turnbull and Baird, 1957). It should be remembered, however, that measurements of oxygen saturation mainly give an indication of the amount of oxygen present in the blood. For a more complete picture of the oxygenation it is also necessary to know the oxygen tension ($pO_2$) since that is the force by which oxygen is pressed from the vessels into the tissues and because the physiological effect of the oxygen depends solely on its $pO_2$.

As oxygen in foetal circulation is obtained from maternal blood in the intervillous space of the placenta, a comparison between the levels of $pO_2$ in the intervillous space and in the umbilical vessels will indicate the diffusion pressure drop of the oxygen between the maternal and foetal circulation in the placenta.

## Material and Methods

The cord blood was investigated in 178 cases after spontaneous delivery in vertex presentation. One hundred and twenty-eight of the infants were normal without any signs of asphyxia; 30 infants had signs of mild asphyxia, usually with slow or irregular heart beats. Nineteen infants had meconium stained amniotic fluid without any other signs of asphyxia.

During labour the mothers were given 'trilene' or nitrous oxide and in some cases a few drops of chloroform at the moment of delivery.

The cord was clamped immediately after birth and blood was drawn from the vein and the arteries into heparinized syringes. The analyses of the blood were started immediately.

The blood in the intervillous space was investigated in 25 cases of normal pregnancy. The placenta was punctured through the abdominal wall before labour had started. Only local anaesthesia was used and no complications occurred. Before puncture the placenta was localized as carefully as possible by palpation and auscultation (Norman, 1953) or sometimes by radiographs. The puncture was always made below the umbilicus on the side of the legs of the foetus. When the placenta was punctured, it was an easy matter to get 10-20 ml. of maternal blood into a heparinized syringe; if the uterine wall only was punctured the outcome was a few millilitres of blood obtained with difficulty. Punctures of the human placenta have also been made by Walker and Turnbull (1959) and Prystowsky (1959).

The $pO_2$ was measured polarographically with the Clark electrode as described by us (Rooth, Sjöstedt and Caligara, 1959). Within the range of $pO_2$ observed here, the error of the analyses should be less than $\pm$ 1 mm. Hg.

Great care was taken in order to obtain as reliable information as possible about the time of gestation. Most of the mothers were under observation by the staff during pregnancy and any case in which the duration of pregnancy was doubtful was rejected from the investigation.

## Results

The $pO_2$ values from the vein are given in Fig. 1 and from the arteries in Fig. 2. In normal cases two-thirds of the observations from the vein are between 25 and 35 mm. Hg; in the arteries two-thirds of the values are between 10 and 20 mm. Hg. The mean $pO_2$ in normal cases is 29·3 in the vein and 18·3 mm. Hg in the arteries.

Figs. 1 and 2 also give the $pO_2$ values for the asphyxiated infants and infants with meconium stained amniotic fluid. The mean $pO_2$ in the vein of the asphyxiated infants is 27·0 and in the arteries 16·0 mm. Hg. The mean $pO_2$ in the vein of the infants with meconium stained amniotic fluid is 29·2 and in the arteries 15·6 mm. Hg.

In Table 1 the $pO_2$ in 113 specimens from the umbilical vein and 89 samples from the arteries are divided according to gestation time. The

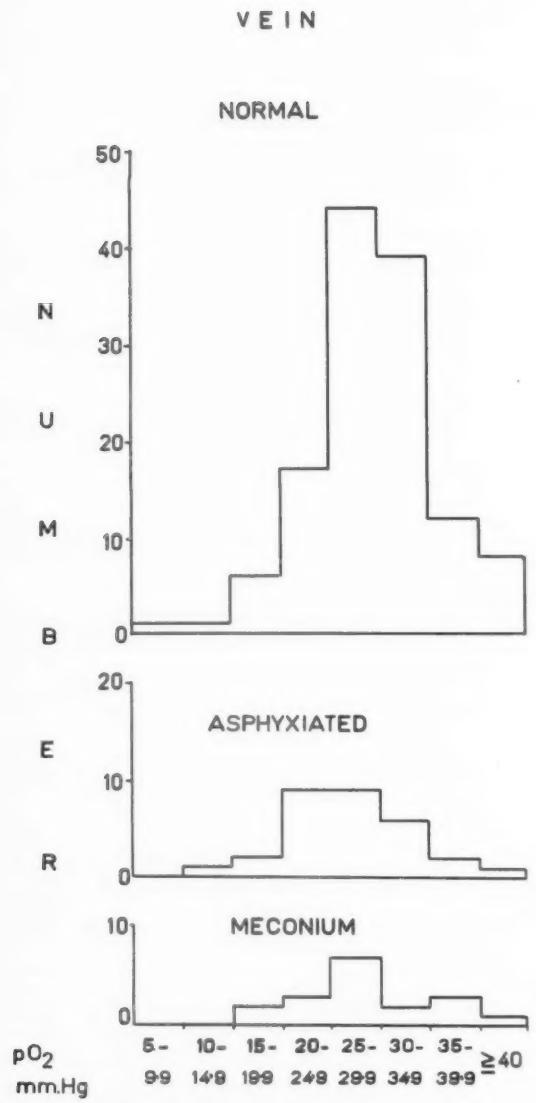


FIG. 1.—Distribution of the oxygen tension in the umbilical vein in normal and asphyxiated infants and infants with meconium stained amniotic fluid.

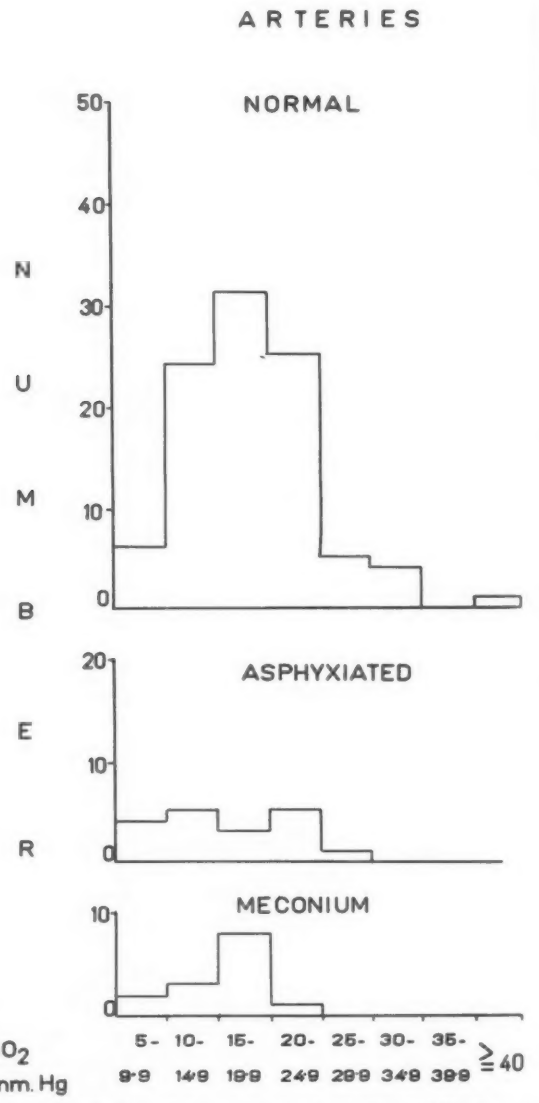


FIG. 2.—Distribution of the oxygen tension in the umbilical arteries in normal and asphyxiated infants and infants with meconium stained amniotic fluid.

differences between the different weeks are small and irregular in the whole group as well as in the primigravidae (Table 2).

The results of the analyses of the intervillous blood are shown in Fig. 3. The mean $pO_2$ is 39·9 mm. Hg with the range 27·5 to 53·7 mm. Hg.

## Discussion

The figures available in the literature on the $pO_2$ of the cord blood are summarized in Table 3. Direct measurements have been made by Beer, Bartels and Raczkowski (1955), Wulf (1958) and Sjöstedt, Rooth and Caligara (1960). Beer *et al.* (1955) and Wulf used the potentiometric method of Bartels (1951). The mean values of Beer *et al.* are lower than might be expected from the oxygen saturation analyses cited above. They are difficult to explain and may be due to the individual cases. On the other hand the values given by Wulf correspond to ours and to the majority of the oxygen saturation measurements in the literature and it may therefore be assumed that the mean $pO_2$ in the umbilical vein in normal cases is about 30 mm. Hg

TABLE 1

OXYGEN TENSION IN THE UMBILICAL CORD BLOOD AFTER NORMAL DELIVERY AT DIFFERENT GESTATION WEEKS

| Gestation (weeks) | Vein | | Artery | | Arterio-venous Difference |
|---|---|---|---|---|---|
| | Number | Mean $pO_2$ (mm. Hg) | Number | Mean $pO_2$ (mm. Hg) | |
| 38 | 4 | 31·8 | 3 | 21·8 | 10·0 |
| 39 | 18 | 28·5 | 12 | 19·9 | 8·6 |
| 40 | 36 | 28·5 | 30 | 18·0 | 10·5 |
| 41 | 25 | 31·2 | 18 | 17·5 | 13·7 |
| 42 | 18 | 29·6 | 15 | 19·3 | 10·3 |
| 43 | 12 | 28·2 | 11 | 16·0 | 12·2 |
| Total .. | 113 | 29·3 | 89 | 18·2 | 11·1 |

at the time of delivery and the corresponding value in the arteries is about 18 mm. Hg.

Wulf shows, as expected, that the $pO_2$ in the cord blood is less in the asphyxiated cases. In the present series the mean difference between the normal cases and both the asphyxiated group and the meconium group is small, but as shown in Figs. 1 and 2 there are more low values in the two latter groups than in the normal cases. In the normal

TABLE 2

OXYGEN TENSION IN THE UMBILICAL CORD BLOOD OF PRIMIGRAVIDAE AFTER NORMAL DELIVERY IN DIFFERENT GESTATION WEEKS

| Gestation (weeks) | Vein | | Artery | |
|---|---|---|---|---|
| | Number | Mean $pO_2$ (mm. Hg) | Number | Mean $pO_2$ (mm. Hg) |
| 38 | 2 | 30·8 | 2 | 9·1 |
| 39 | 13 | 29·2 | 10 | 20·9 |
| 40 | 17 | 28·0 | 14 | 17·6 |
| 41 | 6 | 30·8 | 6 | 20·6 |
| 42 | 8 | 33·7 | 7 | 25·2 |
| 43 | 8 | 29·2 | 6 | 18·2 |
| Total .. | 54 | 29·7 | 45 | 19·9 |

cases there are 19% with a $pO_2$ in the vein of less than 25 mm. Hg, while in the meconium group there are 32% and in the asphyxiated group 40%. The corresponding frequency of values less than 15 mm. Hg in the arteries is 31, 36 and 50%.

Just as was found in our study on the oxygen saturation in the cord blood (Rooth and Sjöstedt, 1955), the group labelled 'asphyxiated' contains some cases with normal and others with lowered $pO_2$. This is explained by the fact that most of our cases of asphyxia only manifested themselves temporarily in the form of foetal bradycardia before birth.

In comparing the values between the normal and the asphyxiated cases it can be seen that the differences are much smaller for the $pO_2$ than they are for the oxygen saturation. This is because of the shape of the oxygen dissociation curve. In measurements of adult arterial blood the oxygen saturation may vary from between 92 to 96%, whereas at the same time the $pO_2$ changes from 70 to 95 mm. Hg. This is because the values lie in the horizontal range of the oxygen dissociation

TABLE 3

SURVEY OF UMBILICAL CORD BLOOD $pO_2$ STUDIES

| Author | Artery | | Vein | |
|---|---|---|---|---|
| | Number | Mean $pO_2$ | Number | Mean $pO_2$ |
| *Normal pregnancy and non-asphyxiated infants* | | | | |
| Haselhorst and Stromberger, 1931 .. | | | 4 | 31·0 |
| Beer *et al.*, 1955 .. | 22 | 9·2 | 24 | 22·4 |
| Wulf, 1958 .. .. | 36 | 15·7 | 36 | 32·0 |
| Sjöstedt *et al.*, 1960 .. | 51 | 16·9 | 68 | 28·9 |
| Present investigation .. | 96 | 18·3 | 128 | 29·3 |
| *Asphyxiated infants* | | | | |
| Wulf, 1958 .. .. | 20 | 4·0 | 20 | 7·3 |
| Present investigation .. | 32 | 15·8 | 49 | 27·9 |

curve. With the umbilical blood the opposite occurs. The values are now in the range of the vertical part of the dissociation curve and although the oxygen saturation changes from 70 to 45% the tension only decreases from 30 to 25 mm. Hg. In this way the already initially low $pO_2$ is maintained, although the oxygen supply is reduced. This has been called the buffering effect of the curve (Barron, 1959).

Most obstetricians associate the presence of meconium staining of the amniotic fluid with intrauterine hypoxia. The present series substantiates this in so far as the $pO_2$ in the cord blood is low more often in the meconium group than in the normal.

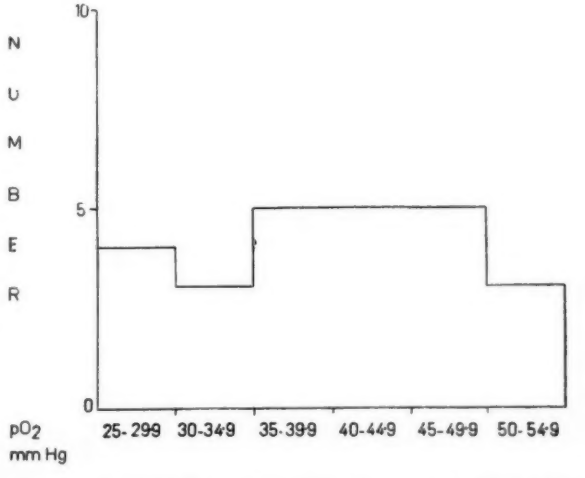


FIG. 3.—Distribution of the oxygen tension in the intervillous blood of the placenta.

According to Walker and Turnbull (1953) advancing gestation time especially after 40 weeks causes a decrease in the oxygen saturation in the cord blood. These results have been confirmed by MacKay (1957), whereas no such change has been observed by MacKinney *et al.* (1955), Bancroft-Livingston and Neill (1957) or Rooth and Sjöstedt (1957). Recently Turnbull and Baird (1957) and Walker and Turnbull (1959) have stated that this decrease only occurs in primigravidae.

In his series Wulf had nine cases of prolonged pregnancy and found the average $pO_2$ in the vein to be 13·3 and in the arteries 9·4 mm. Hg. Since not less than five of these infants were asphyxiated at birth and needed artificial respiration it cannot be concluded from Wulf's data that prolonged pregnancy *per se* decreases the $pO_2$ of the cord blood. In our series of 113 normal infants 45 cases have a gestation time of 41 weeks or more and, as shown in Tables 1 and 2, the $pO_2$ in the umbilical vein and arteries is about the same from the 38th to the 43rd week of pregnancy. The same is valid for primigravidae. Thus it is not possible to demonstrate any physiological change in the $pO_2$ in the umbilical blood immediately before, during or after term.

Nearly all authors have found the arteriovenous difference to be 10-13 mm. Hg (Table 1). Only Wulf has a bigger difference, 16 mm. Hg.

No direct measurement of the intervillous $pO_2$ has been published, but our mean value, 40 mm. Hg, may be compared to that of Prystowsky (1957). Prystowsky measured the oxygen saturation and estimated the $pO_2$ from an oxygen dissociation curve without giving any measurements of *p*H. In eight cases he had a mean of 37·5 mm. Hg with the range 24·0-72·0 mm. Hg. Walker and Turnbull (1959) also measured the oxygen saturation in the intervillous blood and estimated the $pO_2$ to be 36-40 mm. Hg. Beer *et al.* (1955) calculated the intervillous $pO_2$ as 30·2 mm. Hg, basing their figures on their measurements of the cord blood and data on the maternal arterial blood. As their cord blood figures were much lower than ours, as already discussed, it is not surprising to find their figure for the intervillous blood lower than ours.

It seems therefore that the normal foetus gets its oxygen supply from the maternal side of the placenta at a tension of about 40 mm. Hg. It is not yet known whether the observed scatter of $\pm 13$ mm. Hg is due to individual variations in the mother or to fortuitous sampling near or distal to the arterial blood entering the intervillous space.

Given the data on the $pO_2$ of the intervillous blood, umbilical vein and umbilical artery blood it is possible to calculate the mean drop in oxygen pressure between the maternal and foetal circulation, which is defined as the pressure drop between the intervillous space and the mean between the umbilical artery and umbilical vein. We thus find a value of 16 mm. Hg. It should be remembered that in no instance have we measured the individual pressure drop and the figure given here is one based on average normal intervillous blood and average normal foetal blood. Prystowsky (1957), obtaining the cord blood one minute after obtaining the intervillous samples, has been able in three cases to estimate the pressure drop from measurements of the oxygen saturation and found 17·7, 18·3 and 20·4 mm. Hg, i.e. figures of the same order as in our measurements. When the mothers were given oxygen, Prystowsky (1959) found that the mean pressure drop increased to 37·5 mm. Hg. Beer *et al.*, who, as mentioned, have measured $pO_2$ in the cord blood, made ingenious calculations of the intervillous space blood. If their figures are used in the same way to calculate the mean pressure drop it will be 14·4 mm. Hg. From this it seems that the normal pressure drop is somewhere between 15 and 20 mm. Hg. It is noteworthy that this is much higher than the corresponding drop in the alveoli, where it is of the order of a few mm. Hg. One reason for this, besides the obvious anatomical differences, is that when the blood is very hypoxic, as is that of the cord arteries, a long contact time is necessary for complete equilibration, and probably the time in question is too short in the placenta. It is extremely risky to estimate the pressure drop in the tissue between the maternal and foetal circulation in the placenta from the present figures, but at any rate it cannot be higher than the difference between the intervillous blood and the umbilical vein, i.e. 10 mm. Hg. Probably the drop is lower.

## Summary

The oxygen tension in the umbilical vein at the time of delivery in normal cases ranges from 6 to 46 mm. Hg with a mean of 29·3 mm. Hg. In the umbilical arteries the range is from 6 to 32 mm. Hg with a mean of 18·3 mm. Hg.

The mean values in a group of slightly asphyxiated infants in both arteries and vein is a few mm. Hg lower.

The mean value in the umbilical vein is the same in the normal group as in a group of infants with meconium stained amniotic fluid, but the mean value in the arteries in this group is about the same as in the asphyxiated group.

In the intervillous space the mean $pO_2$ in 25 cases is 39·9 mm. Hg.

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# ABSENT UMBILICAL ARTERY*

## A REVIEW OF 113 CASES

BY

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The umbilical cord normally contains two arteries and one vein embedded within Wharton's jelly which is, in turn, enclosed by an epithelial membrane.

Hyrtl (1870) described the absence of one of the umbilical arteries in 12 instances (four infants and eight placentae) of which only two infants were malformed, one suffering from spina bifida and both having cleft palates. He also noted that male infants were affected more often than female infants and that females lacking one umbilical artery were more frequently malformed and often anencephalic. Neither the observation of male dominance nor the higher incidence of abnormalities in females have subsequently been confirmed, although there is a high incidence of anencephalic deformity in the female infants. He collected a total of 58 cases from the literature to add to the 12 of his own.

Browne (1925) reported a premature infant in whom the umbilical cord contained a single artery and the umbilical vein was replaced by a capillary network. Javert and Barton (1952) reported the results of the examination of 1,000 abortuses in which histological sections from 104 umbilical cords were examined. Only one was found to contain a single artery.

Benirschke and Brown (1955) described a retrospective study of 55 infants in whom one artery was missing from the entire length of the umbilical cord. Of these 55 only 13 (24%) were considered to be normal children and of the remaining 42 there were 27 (64%) who suffered from a wide range of congenital abnormalities, many of whom had multiple defects. Placental abnormalities were common (39%). Little (1958) examined the umbilical cords of 1,200 consecutive deliveries, finding that 12 (1%) contained only one artery throughout, and in four (0·3%) the arteries fused locally near the placenta; congenital abnormalities were present in 25%. Recently Benirschke and Bourne (1960) reported the incidence of absent umbilical artery to be 15 (1%) in 1,500 consecutive deliveries. Eight (53%) were considered to be developmentally normal, although one was stillborn, whilst seven (47%) were found to possess major or minor congenital abnormalities. Only 12 (80%) remain alive, one of whom has survived operative treatment for oesophageal atresia and tracheo-oesophageal fistula.

It seems fairly certain that the overall incidence of this abnormality is in the region of 1% of all deliveries. Furthermore, they report that absent umbilical artery occurred seven times (7%) in a series of 100 consecutive unselected twin pregnancies. This is much higher than has hitherto been supposed.

### Materials and Method

A total of 113 infants in whom one umbilical artery was absent (Fig. 1) has been studied at the Boston Lying-in Hospital and the Children's Medical Centre, Boston, Mass. The series is composed of 55 cases first observed in a mainly retrospective study, 15 cases reported to be present in the examination of 1,500 consecutive placentae, together with a further 43 instances observed during the past three years in the Pathology Department of the Boston Lying-in Hospital. With the exception of some of the 55 instances which were retrospective, the examination consisted of a gross evaluation of the placenta together with a microscopic study of at least three blocks of tissue. These included sections from the middle portion of the umbilical cord, a segment of rolled membrane and a section of full thickness placental tissue. In the event of absence of an umbilical artery from the histological section of the cord, the secundines, which had been

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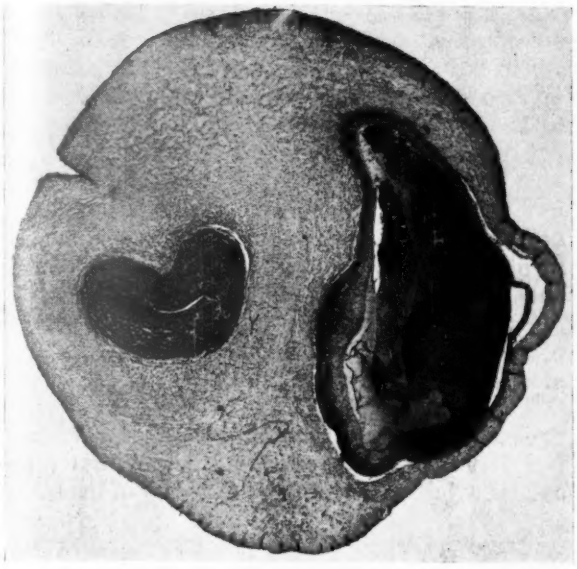

FIG. 1.—Absence of one umbilical artery. Section of the umbilical cord showing the dilated vein and a single artery. Note the muscular wall and small lumen of the artery. There are no residual ducts or vessels present. (H. and E. × 10.)

stored awaiting 'histological clearance', were re-examined to confirm the absence of an artery from the entire length of the cord. In instances of foetal death confirmation of the absence of one of the intra-abdominal vessels was sought at necropsy. Owing to the high incidence of associated congenital abnormalities, it was the usual practice to inform the paediatrician immediately upon the finding of a single umbilical artery. This assisted in the early diagnosis of oesophageal atresia in at least one infant.

A total of approximately 6,000 deliveries occur each year in the Boston Lying-in Hospital. With the exception of the consecutive series mentioned above the placentae are examined in the laboratory only when indicated by such conditions as maternal illness or disease; foetal distress, abnormality or prematurity; plural pregnancy; hydramnios and other complications of pregnancy as well as patients of clinical or pathological interest.

It is realized that 98 of the total 113 cases are derived from selected material from which it might be erroneous to draw definite and final conclusions. The reasons for the selection of the material from which these cases are derived, however, are so diverse that there is ample justification for the analysis of certain factors.

### Maternal Factors

**Age.** An analysis of the ages of the 113 mothers who were delivered of infants lacking one umbilical artery is shown in Table 1. It is noticeable that 26 (62%) of the 42 primigravidae were under the age of 25, whereas only 13 (22%) of the 59 multigravidae were under the same age. Compared with the average ages of a control series of patients, this series shows an increased incidence of the anomaly among the younger primigravidae and the older multigravidae. The age groups of the total series, however, conform fairly closely to those of the controls, because the increased incidence at the younger end of the primigravidae scale balances the similar, but less well marked, rise at the older end of the multigravidae scale. These findings are in broad agreement with Baird and Walker (1959), who state 'The incidence of foetal deformity . . . is highest in the 15-19 age group and decreases with age till thirty-five; a slight rise occurs in the age group 35 and over'.

The average age of the 19 mothers of infants with central nervous system anomalies, 28·3 years compared with 28·5 years, failed to confirm that these, in particular, occur in a high age group (Hegnauer, 1951).

**Parity.** Forty-two of the mothers were primigravidae and 59 were multigravidae whose parity varied from one to 15. These are shown in detail in Table 2 and agree essentially with the control series except for the high number pregnant for the

TABLE 1

ANALYSIS OF AGES OF MOTHERS DELIVERED OF INFANTS LACKING ONE UMBILICAL ARTERY

| Age (years) | Primigravida | Multigravida | Total |
|---|---|---|---|
| 20 | 5 | 1 | 6 |
| 21–25 | 21 | 12 | 33 |
| 26–30 | 8 | 15 | 23 |
| 31–35 | 6 | 17 | 23 |
| 36–40 | 2 | 12 | 14 |
| 41 | — | 2 | 2 |
| Total .. .. | 42 | 59 | 101 |
| Average age .. | 25·3 | 30·7 | 28·5 |

TABLE 2

GRAVIDITY

| Gravidity | No. |
|---|---|
| 1 | 42 |
| 2 | 21 |
| 3 | 15 |
| 4 | 11 |
| 5 | 3 |
| 6 | 5 |
| 7 | 1 |
| 8 | 2 |
| 15 | 1 |
| Total .. | 101 |

sixth time, an observation that is not considered to have any significance.

The 59 women who had been pregnant previously had produced a total of 111 live born infants, 12 stillbirths (a rate of 103 per 1,000) and 32 abortions. Four of the 111 live born infants died in the newborn period so that only 107 (69%) infants survived the newborn period out of a total of 155 previous pregnancies. This incidence (31%) of foetal loss in the past history of these patients is surprisingly high and much greater than the 11% of the control series.

**Maternal Diseases.** A high incidence of pre-eclampsia (30%) was described by Benirschke and Brown (1955). This was not confirmed by Little (1958). Both authors agree that the large number of pre-eclamptic patients in Benirschke's series was the result of material selection and that it did not reflect the true incidence of this complication of pregnancy. This series of 113 cases includes the 55 described by Benirschke, together with a further 58 additional cases in which pre-eclampsia was diagnosed in only five (9%) instances. This indicates that pre-eclampsia is not associated with the absence of an umbilical artery either as an aetiological factor or as a result of the abnormality. Altogether a total of 19 patients (16%) were found to be suffering from pre-eclampsia in the total of 113.

The association, however, of pre-eclampsia and a single artery in a total of 19 patients resulted in seven stillbirths, three neonatal deaths and nine living infants, which illustrates that this combination, even if it is fortuitous, is particularly lethal to the foetus.

A careful study of the general health of the mothers has not disclosed any factor that might influence the pregnancy so as to predispose the foetus to this particular anomaly. The high incidence of foetal wastage in the previous pregnancies of multigravida has been described; a high proportion (8%) of patients suffered from antepartum haemorrhage.

Two otherwise normal infants suffered from erythroblastosis foetalis due to rhesus incompatibility, one being stillborn and the other dying on the first day. Four of the mothers suffered from epilepsy (*grand mal*).

**Hydramnios.** The incidence of foetal abnormality is particularly high in association with hydramnios. Macafee (1950) stated that the incidence of foetal abnormality was 46% in a series of hydramniotic pregnancies. It is not surprising, therefore, that there should be a fairly high incidence of hydramnios in association with absence of an umbilical artery. Nineteen (19%) patients were considered to suffer from hydramnios in the 101 in whom adequate information was available and this figure is probably a conservative estimation, because in the original study of 55 cases only four were present, 15 occurring in the last 58 patients. This high incidence of hydramnios was not confirmed by Little (1958). It is interesting that all 19 (100%) of these infants suffered from congenital abnormalities and that 12 were stillborn; five died in the neonatal period and the two who survive do so because of successful surgical treatment of oesophageal atresia. The association between hydramnios and oesophageal atresia is now accepted (Scott and Wilson, 1957), and in one of the surviving patients the early diagnosis of oesophageal atresia was hastened by the finding of umbilical artery aplasia within a few hours of the birth of the infant.

**Heredity.** There is little or no evidence to show that this condition is of an hereditary nature. Only one mother was known to suffer from any major congenital abnormality (pulmonary stenosis) and one had congenital syphilis. No abnormalities were known to be present in the male parents but they were, necessarily, not subjected to the same scrutiny as the mother. Furthermore, the wide range of associated congenital abnormalities seems to mitigate against a single hereditary factor. Four mothers (4%) suffered from *grand mal*, which might be significant, but the numbers are too small to justify the assumption that it was in any way a causative factor.

There is, however, some evidence that the anomaly forms part of a diathesis in which abnormalities are frequently multiple and may be recurrent. These assumptions are based upon the past history of 59 multigravid patients in which 48 (31%) out of a total 155 pregnancies failed to produce a living child. It is unfortunate that more detail was not available concerning the loss of these infants, but such information as is available does not reveal any definite recurrence of single umbilical artery abnormality, although several are known to have produced abnormal infants previously. Several mothers have subsequently produced normal children, all of whom possessed two umbilical arteries. That these patients experience a greater than average difficulty in producing living normal children is definite and it is possible that the finding of arterial abnormalities in the umbilical cord may lead to the recognition of such 'high-risk' patients even in their first pregnancy. The parents of one infant were known to be related cousins; there was no other recorded evidence of consanguinity.

TABLE 3
DETAILS OF 15 (1%) AFFECTED INFANTS FROM 1500 CONSECUTIVE DELIVERIES

| Number | Sex | Twins | Gestational Age (weeks) | Complication of Pregnancy | Foetal Anomalies | Follow-up |
|---|---|---|---|---|---|---|
| 1 | M | — | 35 | Chorioamnionitis | None found | Not traced |
| 2 | F | — | 39 | Placental infarct | None found | Normal |
| 3 | F | F/F monochorial | 38 | None | Forked xyphoid | Normal development |
| 4 | M | — | 42 | Irregular heart 0–130; discharge meconium | None found | Normal |
| 5 | M | M/M monochorial | 38 | 650 g. lighter than other twin | Hydrocele, abnormal cardiac rhythm | Developing normally; bigger than twin |
| 6 | M | — | 38 | None | Slight club foot—right | Normal development |
| 7 | F | — | 40 | None | None found | Normal |
| 8 | F | F/M dichorial | 38 | None | Hyperteleorism, short fingers | No problem |
| 9 | F | — | 37 | Hydramnios | Oesophageal atresia and fistula, sacral anomaly | Operated, survived |
| 10 | F | — | 37 | Hydramnios | Anencephaly | Stillborn |
| 11 | F | — | 40 | None | None found | Normal |
| 12 | F | — | 40 | None | None found | Normal |
| 13 | M | — | 37 | None | Renal agenesis, atresia ani, accessory pancreas, equinovarus | Died |
| 14 | F | — | 37 | Maternal floor infarction; long cord | None found | Stillborn |
| 15 | F | — | 40 | Long cord | None found | Not traced |

(After Benirschke and Bourne, 1960.)

## The Infants

**Incidence.** In the examination of a series of 1,500 consecutive placentae a total of 15 (1%) of the umbilical cords were found to contain only one artery throughout their length. Seven (46%) of these 15 infants suffered from congenital abnormalities, of which three were of major significance (Table 3). One was a stillborn anencephalic and one died from renal agenesis. There were eight (53%) normally developed infants of which one was a macerated stillbirth in whom no congenital abnormality could be found.

The overall mortality in this short series is three out of 15 (20%) with one further child surviving operative repair of an oesophageal fistula and atresia.

The relatively high incidence of twin infants in this consecutive series (20%) is confirmed to some extent by the fact that in a series of 100 consecutive twin deliveries an absent umbilical artery was present seven (7%) times. The overall incidence of one in 100 is confirmed by Little (1958) and by Bourne (1961) who recognized the condition five times in 475 (one in 95) consecutive umbilical cords. A similar incidence is also reported by Emig (personal communication).

**The Fate of the Infants.** It is realized that the total series of 113 cases is partially selected, but nevertheless an analysis of these patients is very informative. Table 4 shows the fate of these infants.

**Alive Infants.** Only 48 (42%) are alive, of whom 14 (29%) are known to suffer from congenital abnormalities; 27 infants were either seen or were considered by their medical attendant to be both physically and mentally normal. It was impossible to trace seven infants, all of whom, according to their records, were normal when last examined. In the absence of any information to the contrary these infants are considered to be living and normal.

TABLE 4
FATE OF THE INFANTS

| Infants | Nos. | % |
|---|---|---|
| Total | 113 | 100 |
| Alive | 48 | 42 |
| Normal infants | 34 | |
| Known congenital abnormality | 14 | |
| Dead | 65 | 58 |
| Congenital anomaly incompatible with life | 39 | |
| Congenital anomaly compatible with life in infants dead of other causes | 5 | |
| Possible anomaly in unexamined infants | 15 | |
| No anomaly | 6 | |

It has been possible to trace all 14 infants who are alive and who suffer from congenital abnormalities of varying severity. Several of these infants (Table 5) are not expected to reach adult life and two survive only because of successful surgical repair of oesophageal atresia.

**Dead Infants.** Sixty-five (58%) of the infants died or were born dead, of whom 59 (91%) were suffering from definite or probable congenital abnormalities (Table 4), and only six (9%), who died of known causes, were considered to be normally developed for their maturity.

TABLE 5

KNOWN ABNORMALITY COMPATIBLE WITH LIFE IN 14 SURVIVORS

| Maturity (weeks) | Weight (lb.) | Sex | Abnormality | Follow-up (years) | Remarks |
|---|---|---|---|---|---|
| 40 | 7·1 | F | Congenital heart disease | 17 | Twin |
| 41 | 5·1 | M | Oesophageal atresia | 6 | Successful operation |
| 36 | 7·1 | M | Brain cysts | 4 | Very poor prognosis |
| 37 | 5·11 | M | Hydrocele, umbilical hernia, inguinal hernia | 4 | |
| 32 | 3·6 | M | Mental defect; optic fundi abnormal | 3 | Poor prognosis |
| 42 | 4·15 | F | Multiple haemangiomata | 2 | |
| 42 | 6·2 | M | Arthrogryphosis multiplex cystica, cryptorchid | 2 | |
| 32 | 2·5 | M | Cryptorchid | 2 | Twin |
| 39 | 8·0 | F | Marfan's syndrome: arachnodactyle | 1 | |
| 38 | 5·13 | M | Sternal abnormality | 1 | Twin |
| 38 | 3·2 | M | Cardiomegaly (?) cause | 1 | Twin |
| 38 | 5·8 | M | Talipes equinovarus | 0·6 | |
| 38 | 5·1 | F | Hyperteleorism | 0·5 | Twin |
| 36 | 4·6 | F | Oesophageal atresia | 0·5 | Successful operation |

Congenital abnormality of such a major degree as to be incompatible with life was present in 39 (60%) of these children, whilst five (8%) who died from other causes were suffering from anomalies that probably contributed to their death, and 15 (22%) were considered to be suffering from a congenital abnormality, although severe maceration or lack of a post mortem examination prevented exact diagnosis.

Absence of one umbilical artery seems, in itself, to be a simple and innocuous congenital abnormality, but it is associated with a perinatal mortality involving 58% of the affected infants, together with a further 12% who are alive but abnormal in some way. Such a relationship is considered to be significant.

**Congenital Abnormalities.** The types of congenital abnormality from which the affected infants suffered have been classified into systems. These are listed in Table 6 and they are detailed in Table 7.

The majority of the babies suffered from multiple defects which, if serious, are listed separately so that the total is greater than the number of infants concerned. No system or peculiar abnormality is particularly prominent, although aplastic lesions of

TABLE 6

CONGENITAL ABNORMALITIES

| Abnormalities | Nos. | % |
|---|---|---|
| Known congenital abnormalities (mostly multiple) | 58 | 51 |
| Gastro-intestinal | 31 | |
| Skeletal | 28 | |
| Genito-urinary | 27 | |
| Cardiovascular | 21 | |
| Neurological | 19 | |
| Others | 10 | |
| Possible abnormality (unexamined, dead) | 15 | 14 |
| No known abnormality | 40 | 35 |
| Total number of cases | 113 | 100 |

TABLE 7

DETAILS OF CONGENITAL ABNORMALITIES

| Abnormality | Nos. |
|---|---|
| Gastro-intestinal | 31 |
| Oesophageal atresia | 8 |
| Imperforate anus | 6 |
| Exomphalos | 5 |
| Malrotation of gut | 4 |
| Herniae | 4 |
| Cleft palate | 3 |
| Cysts of larynx | 1 |
| Skeletal | 28 |
| Talipes equinovarus | 9 |
| Poly and syndactyle | 6 |
| Spine (excluding spina bifida) | 5 |
| Phocomelia | 2 |
| Arthrogryphosis | 2 |
| Achondroplasia | 1 |
| Arachnodactyle | 1 |
| Congenital dislocation hip | 1 |
| Microphthalmia | 1 |
| Genito-urinary | 27 |
| Sexual aplasia | 5 |
| Renal aplasia | 5 |
| Polycystic kidneys | 4 |
| Undescended testes | 3 |
| Megaloureters | 3 |
| Hypospadias | 2 |
| Cryptorchid | 2 |
| Recto-vaginal fistula | 1 |
| Clitoral hyperplasia | 1 |
| Double uterus | 1 |
| Cardiovascular | 21 |
| Interventricular defect | 5 |
| 'Congenital heart disease' | 5 |
| Fallot tetralogy | 4 |
| Triloculare | 3 |
| Cardiomegaly | 2 |
| Coarctation of aorta | 1 |
| Absent valves | 1 |
| Neurological | 19 |
| Anencephaly | 5 |
| Hydrocephaly | 4 |
| Spina bifida | 4 |
| Mental defect | 2 |
| Angioma | 1 |
| Brain cysts | 1 |
| Cyclops | 1 |
| Nerve paralysis | 1 |
| Others | 10 |
| Turner's syndrome | 2 |
| Hyperteleorism | 1 |
| Haemangiomata | 1 |
| Pulmonary aplasia | 1 |
| Splenomegaly | 1 |
| Asplenia | 1 |
| Abnormal optic fundi | 1 |
| Cystic pancreas | 1 |
| Cystic liver | 1 |

TABLE 8

INFANTS DEAD OF ABNORMALITIES INCOMPATIBLE WITH LIFE

| Abnormality | Stillborn | Neo-natal Death | Total |
|---|---|---|---|
| Anencephaly .. .. .. | 5 | — | 5 |
| Hydrocephaly .. .. .. | 2 | 2 | 4 |
| Exomphalos .. .. .. | 1 | 1 | 2 |
| Congenital heart disease .. | 4 | 11 | 15 |
| Cyclops .. .. .. .. | 1 | — | 1 |
| Cranial nerve paralysis .. .. | — | 1 | 1 |
| Spina bifida .. .. .. | — | 4 | 4 |
| Renal aplasia .. .. .. | 1 | 2 | 3 |
| Gastro-intestinal aplasia .. | — | 4 | 4 |
| Total .. .. .. | 14 | 25 | 39 |

TABLE 9

KNOWN ABNORMALITIES IN INFANTS DEAD OF OTHER CAUSES

| Cause of Death | Abnormality |
|---|---|
| Broncho-pneumonia | Syndactyle |
| Hyaline membrane | Tracheo-oesophageal fistula |
| Stillborn macerated | Unilateral renal hypoplasia |
| Stillborn macerated | Cleft palate |
| Stillborn macerated | Talipes equinovarus |

the alimentary and genito-urinary tracts are more frequent, and lesions of the central nervous system less frequent than might be expected.

Thirty-nine infants died of congenital abnormalities incompatible with life (Table 8). Congenital heart disease is the most common abnormality considered incompatible with life. Table 9 shows the anomalies present in those five infants whose death was considered to be due mainly to other reasons.

The congenital abnormalities from which the surviving infants suffer together with their weight and maturity at birth, sex, period of follow-up and comments are shown in Table 5. Several of these children will not survive to reach adult life. Eight (57%) were premature by weight although only two (14%) were born before the 36th week of gestation. This is not surprising if the absence of an umbilical artery slows the actual growth of a foetus *in utero*, but it does not necessarily prevent the foetus from maturing. It is upon maturation rather than actual body weight that the infant subsequently depends for its survival.

Trivial abnormalities such as cutaneous naevi and minor haemangiomata have not been included in this series. The number of uncomplicated or single malformations is very low. There are only 14 (24%) whilst the number of multiple abnormalities, 44 (76%) is much higher than expected. The great increase in the incidence of congenital abnormalities in this series is due mainly, but not entirely, to a rise in the number of multiple abnormalities. Neel (1958) found that only 14·9% of malformed children had multiple defects; Schull (1958) reported that the percentage of infants with multiple abnormalities rose to 34·3% if the parents were related.

**Sex.** It was suggested by Hyrtl (1870) that there is a male preponderance associated with this abnormality. This was not supported by Benirschke and Brown (1955) or Little (1958), nor is it supported in the present series, which contains 55 female and 49 male infants. There is one hermaphrodite and the sex of eight infants is not recorded. An analysis of the various abnormalities, the stillbirths, surviving infants or maturity also fails to show any sex domination (other than those which are expected, such as the anencephalic infants, all five of whom were female). There is, in this series, a total of 16 twin infants, whose sex is predominantly female. There are, in fact, 13 female and three male infants. No reason is offered for this apparent female dominance, which despite the small number of cases, does appear to be significant.

**Side of Absence.** It is only possible to define the absent side at necropsy. Unfortunately adequate information is available upon only 22 infants in whom the artery was absent, 12 times on the right side and 10 times on the left. The intra-abdominal part of the umbilical artery was easily recognizable in more than half the babies, although in some it existed as a very thin threadlike structure. Fig. 2 demonstrates absence of the right artery. The dissection displays the branches of the aorta as seen from the dorsal aspect and shows marked aplasia of all the aortic branches on the right side. A similar developmental abnormality of these vessels was frequently noted at necropsy, but the corresponding lower limb was never smaller than the contralateral limb. When present, deformities of the lower limbs were usually more severe upon the affected side.

**Maturity and Weight.** The maturity of 109 infants is known out of a total of 113. Six were non-viable, i.e. born before the 28th week of pregnancy, and 103 were viable. Table 10 shows the maturity, sex, average birth weight and average placental weight of the infants. The average birth weight is lower than normal, especially in the more mature age groups. The average placental weight is also less than normal. It seems reasonable to suppose that the absence of an umbilical artery could cause a diminution of oxygen supply to the foetus and this theory receives some support from the small average foetal weight. There is, however, no compensating enlargement of the placenta.

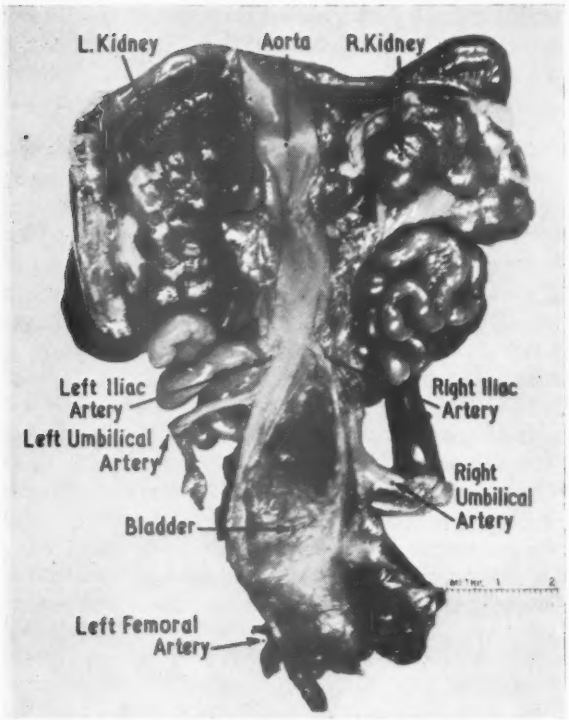


FIG. 2.—The viscera of a stillborn infant dissected and photographed from the dorsal aspect. The aorta is normal. The left iliac, umbilical and femoral arteries are normal. The right common iliac artery, which is about one quarter of its normal size, is distributed mainly along its internal iliac branches. The right umbilical and femoral arteries have no visible lumen and exist as threads in connective tissue.

Infants suffering from congenital abnormalities tend to be born prematurely and in this series 56 (59%) of the 95 viable infants of known weight were premature by weight at birth.

TABLE 10
MATURITY, SEX AND AVERAGE BIRTH WEIGHT OF INFANTS WITH AVERAGE PLACENTAL WEIGHTS

| Maturity (weeks) | Number | Sex (if known) | | Average Birth Weight | | Average Placental Weight (oz.) |
|---|---|---|---|---|---|---|
| | | M | F | lb. | oz. | |
| <28 | 6 | 2 | 1 | — | | — |
| 28 | 2 | 1 | 1 | 1 | 8 | 8 |
| 29 | 2 | | 1 | 1 | 4 | 10 |
| 30 | 2 | 1 | 1 | 2 | 15 | 12 |
| 31 | 1 | — | 1 | 2 | 12 | 9 |
| 32 | 5 | 2 | 3 | 2 | 12 | 13 |
| 33 | 4 | 2 | 2 | 3 | 11 | 14 |
| 34 | 3 | 2 | 1 | 2 | 14 | 12 |
| 35 | 12 | 5 | 7 | 3 | 13 | 15 |
| 36 | 9 | 5 | 3 | 5 | 4 | 18 |
| 37 | 11 | 5 | 6 | 5 | 2 | 14 |
| 38 | 11 | 6 | 5 | 6 | 5 | 15 |
| 39 | 7 | 3 | 4 | 6 | 13 | 17 |
| 40 | 20 | 8 | 12 | 6 | 5 | 22 |
| 41 | 6 | 3 | 2 | 6 | 7 | 19 |
| 42 | 6 | 3 | 3 | 5 | 12 | 14 |
| >42 | 2 | — | 2 | 5 | 0 | 17 |
| Not known | 4 | | | | | |
| Total .. | 113 | 48 | 55 | | | |

**Placentae.** A relatively high incidence of placental abnormality was recorded by Benirschke and Brown (1955), and Little (1958) reported an increased frequency of velamentous insertion of the umbilical cord. In this series there was a total of 32 (29%) placentae that showed gross abnormality including, velamentous insertion of the cord (12); circummargination (five); circumvallation (five); lobed (four); placenta praevia (three) and maternal floor infarct (three). Massive infarction of the maternal surface of the placenta with resulting intra-uterine asphyxia has been noted by Benirschke and Bourne (1960) to occur in successive pregnancies and to be associated with absence of an umbilical artery.

Accidental ante-partum haemorrhage occurred in six pregnancies from which only one infant survived; four were stillborn and one died after 24 hours. Placenta praevia was present on three occasions. A history of threatened abortion was given by eight patients, an episode which did not appear to affect adversely the infant's chance of survival.

**Twins.** The incidence of absent umbilical artery is greatly increased in plural pregnancy. In the present series of 113 babies the abnormality occurred 16 times (14%) in twin pregnancies; only five (31%) of these 16 infants are alive and well.

In a consecutive series of 100 twin pregnancies the abnormality was present on seven occasions. This incidence of 7% of twin pregnancies, or 3·5% of twin infants, as compared with an overall incidence of 1% appears to be a significant increase. A similar unexplained observation (Stevenson, Worcester and Rice, 1950) is the finding of a doubled incidence of foetal malformation in twin pregnancies.

Benirschke and Bourne (1960) considered that the increase of this anomaly might be caused by a relatively higher proportion of monozygous twins. This appeared to be correct in a smaller number, but the present larger series of 16 infants does not support the theory. Six (37%) infants were monozygous because of monochorial placentation, while 10 (63%) were dizygous because of dichorial placentation or heterosexual twins, so that they obey the general rule regarding the zygosity of twins, which states that nearly one-third are monozygous and two-thirds dizygous.

## Discussion

Variations in the number of vessels in the umbilical cord are known to occur, but the available information upon their origin and significance is sparse. The

most important vascular aberration is absence of one of the two umbilical arteries through the length of the umbilical cord and is associated with atresia of the corresponding intra-abdominal portion of the artery. This abnormality is present in 1% of pregnancies and in 7% of twin pregnancies. Anastomoses between the umbilical arteries normally occur at the placental end of the umbilical cord either in the cord itself or in the adjacent placenta. These anastomoses presumably serve to equate the intra-arterial pressures and ensure equal distribution of blood throughout the placenta. They may also act as an arterial shunt when a portion of the foetal placental circulation is closed for physiological or pathological reasons and could, therefore, exert a profound influence upon the ability of the foetus to maintain its placental reserve or to resist the anoxic effects of large placental infarcts.

**Foetal Abnormalities.** The incidence of congenital abnormality amongst an average population is between 1% and 2·5% of all live and stillbirths (Malpas, 1937; Logan, 1951; Lewis, 1956) of which approximately half are gross foetal abnormalities. Absence of one umbilical artery appears to be the commonest major congenital abnormality of the human foetus.

There is a significant rise in the incidence of congenital abnormalities associated with foetuses having only one umbilical artery. The width of the range of the congenital abnormalities suggests that the absence of an umbilical artery is not a secondary effect but is probably a primary lesion to which, some at least, of the associated anomalies are secondary.

It is possible that these abnormalities are the result of the hypoxia to which the foetus is subjected during the organo-genetic period. The efficiency of a single artery or the date of closure of a second artery, are not standard so that both the time and degree of relative oxygen lack would vary widely. There is no suggestion that all the anomalies in this series are caused by a single agent, as some are considered to be hereditary (Potter, 1952) but, if a factor such as anoxia were playing a part in their production, it would have to be capable of acting over a long period in order to account for the wide variety of abnormalities concerned.

However, the majority of anencephalic infants possess two normal umbilical arteries, which indicates that either absence of an umbilical artery has no teratogenetic influence, or, if it does, that there are other agents which are equally effective. Similar arguments can be forwarded concerning the other abnormalities of this series, in that they also are considered to occur in the presence of two normal umbilical arteries so that the precise embryological and developmental significance of absence of one umbilical artery is unknown.

The high incidence of associated foetal abnormality occurring in babies with only one umbilical artery suggests that the 'anomalies' are in some way connected. The presence of only one artery in the umbilical cord may constitute a severe impediment to normal foetal development by causing a resistance to the blood flow and possible lack of oxygen to the foetus. This, together with an absence of the juxtaplacental umbilical arterial anastomosis, may also be a cause of intra-uterine death. This series includes 16 twin infants and the fact that 14 (88%) of these infants were smaller than their normal siblings does support the theory that a single umbilical artery impairs normal growth.

Minor congenital abnormalities are conspicuous by their absence in this series. When two factors that are known to be associated with major congenital abnormalities are combined, such as hydramnios and absent umbilical artery, the foetal loss is particularly high.

**Cardiac Malformation.** There are several reasons why a high incidence of cardiac abnormalities might be associated with absent umbilical artery. In itself the absence is an anomaly of the cardiovascular system and other changes may occur because the artery normally develops during the period of rapid formation of the circulatory system. A heavy strain would certainly be imposed upon the heart if a functioning artery underwent degeneration in early foetal life. It has been shown that a single artery can support an apparently normal foetus but the resistance to blood flow and degree of cardiac overload must, at times, be considerable and may predispose to abnormalities within the heart. One might assume that measuring the diameter of the remaining artery would offer some means by which one could determine if an increased resistance to blood flow had existed in intra-uterine life. Unfortunately, the thick muscular wall causes their lumina to vary greatly after delivery, so that there is no reliable method whereby their functional efficiency within the uterus can be assessed (Reynolds, 1952).

**Aetiology.** It is disappointing that even such a large series does not give any definite indication of the cause of this abnormality. There is no definite evidence that the condition is familial or recurrent, although it does occur in the children of women who have a poor reproductive ability. It is more

frequent in the younger primigravida and the older multigravida. The fact that four mothers suffered from epilepsy is interesting but the number is too small to be significant.

We have considered the possibility that the vessel which was formed in a normal manner has subsequently ceased to function, and atrophied. Such a cessation of function would cause some anoxia, however transient, which could easily disturb the embryological development of the foetus and cause congenital abnormalities. The time at which the artery ceased to function would be the teratogenetic termination period and as such would determine which foetal organs would be most severely affected. If the time varied widely, so would the malformation.

The theory that the artery once was present and functioning is supported to some extent by the invariable presence of an intra-abdominal umbilical artery, albeit often attenuated, on the affected side. It is, however, difficult to accept that a properly functioning umbilical artery could entirely disappear from the umbilical cord without leaving some histological evidence of its presence. In four instances, however, the residual arterial structure was present and, having a diameter much greater than that of the vitelline vessels, it is assumed that these remnants are aplastic umbilical arteries.

It is our opinion that the second umbilical artery was never satisfactorily formed within the umbilical cord in the majority of the infants in this series but, that in a few instances, a functioning vessel was present at some stage of foetal development.

**Clinical Importance.** Absence of an umbilical artery, occurring in 1% of patients, is associated with a high incidence of foetal abnormality (65%). Many of these abnormalities are not obvious, nor are they readily apparent upon simple general examination of the newborn. In most maternity units the placenta, membranes and umbilical cord are examined, weighed and measured and it would be a simple procedure to examine routinely the cut end of the cord. The vessels are easily identified and the finding of a single artery should stimulate a further and more detailed examination of the infant. Such an observation might be of great benefit if the presence of unsuspected abnormality were to be considered in those cases of single umbilical artery encountered. Benirschke and Bourne (1960) report that the diagnosis of oesophageal atresia was made six hours after delivery in an infant who was re-examined following the reported finding of a single umbilical artery. The child is well one year after surgical treatment for the condition. The importance of hydramnios in association with absent umbilical artery is stressed, for, in this series, all of the 19 infants in whom this combination was present suffered from a major congenital abnormality.

**Prognosis.** Details of the congenital abnormalities suffered by the affected children have been recorded together with the prognosis both before and after delivery. Absence of one umbilical artery does in itself diminish a child's chance of survival. The incidence of intra-uterine asphyxia, stillbirth and prematurity is higher than normal. The anomaly appears to cause a slowing of intra-uterine growth so that the average birth weight is less than the expected normal average. It is interesting to note that these infants, when healthy, are similar to twin infants in this respect because their ability to survive depends more upon their maturity than weight. This series produces further confirmation that this principle applies also to the single pregnancies.

When the infants are born alive their prognosis is identical to that of their associated abnormality, if present, together with superimposed prematurity. As stated above, they withstand prematurity fairly well and, having survived the newborn period, they develop physically and mentally into normal children, provided, of course, that they are not encumbered by the frequently associated congenital abnormalities.

## Summary

A total of 113 cases of absence of one umbilical artery are presented and analysed, together with a review of the literature.

The abnormality is slightly increased amongst the younger primigravidae and the older multigravidae, but does not increase in incidence as parity rises. A total of 59 multiparous women had had 155 previous pregnancies from which only 107 (69%) infants survived. A total foetal loss of 48 (31%) is considered excessive and indicates that these women, as far as reproduction is concerned, belong to a high risk group. Hydramnios occurred 19 times; all (100%) the infants suffered from major congenital abnormalities and only two survive as a result of surgical treatment for oesophageal atresia. There is, at present, no evidence to show that the condition is hereditary.

The incidence of absent umbilical artery is 1% of all births and 7% of twin pregnancies.

The foetal loss in a consecutive series was 20% but in the total of 113 instances the foetal loss was 65 (58%). Fourteen of the 48 infants who survive are known to suffer from congenital abnormalities.

Major congenital abnormalities were present in 58 (51%) of the infants; only 40 (35%) were developmentally normal and a further 15 (14%) were thought to suffer from a congenital anomaly. The abnormalities were mostly multiple and not confined to any particular system. Obstructive lesions or atresia of the gastro-intestinal and urinary tracts were relatively common.

Fifty-six (59%) of the 95 viable infants of known weight were premature by weight at birth, but the average weight of all the infants at birth was less than normal. The placenta was considered to be abnormal in 32 (29%) of the pregnancies.

It is suggested that routine examination of the cut end of the umbilical cord at delivery might result in early diagnosis of some of the associated congenital abnormalities.

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### Addendum

Since writing this article it has been discovered that one of the infants considered to be developmentally normal is, in fact, suffering from a marked degree of mental retardation.

# THE NUMBER OF ALVEOLI IN THE TERMINAL RESPIRATORY UNIT OF MAN DURING LATE INTRAUTERINE LIFE AND CHILDHOOD

BY

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Until recently the child's lung was considered to be a miniature of the adult lung (Kölliker, 1881). Broman (1923) demonstrated that the bronchial tree underwent further branching after birth (in cows), that foetal alveolar ducts became bronchioles and that there was a postnatal increase of over 30% in the number of subpleural vesicles in the middle lobe of the right lung in rabbits and man.

Much work has been done on the minute structure of the terminal pulmonary units, of which Miller's book (Miller, 1947) is a landmark. Most of the research has been carried out on animals and no one, as far as we are aware, has worked on more than 15 children's lungs. No attempt appears to have been made to estimate postnatal alveolar growth on a quantitative basis. The present report records a statistical survey of the growth of the human terminal respiratory unit during the latter half of intrauterine life and through childhood.

## Material and Methods

The lungs for study came from 2,500 necropsies carried out by the Department of Pathology at the Children's Hospital, Sheffield, during the years 1950-59. The routine necropsy practice at this hospital is to fix the lung while still attached to the heart and trachea. A block of tissue is then taken from each lobe at right angles to the direction of the main bronchus and at a distance of approximately one-third from the root of the lung to the periphery. If pathological lesions are suspected elsewhere in the lung, further blocks are taken.

The whole of the material was surveyed and the sections divided into categories indicating whether or not the lung showed gross pathology, and whether the tissues were well preserved and suitable for detailed study. The clinical histories were surveyed and all cases in which there was a congenital deformity of the heart, or a gross deformity of any other organ, were eliminated. This left approximately 600 well preserved lungs from apparently normally formed children. (Lungs showing a small amount of oedema or areas of partial collapse were not eliminated provided the tissues were well preserved.)

Owing to the high mortality around birth all the lungs from older children were used and a random selection, based on necropsy number, from those dying during 36-40 weeks gestation. When the lungs were presented for histological assessment, the person examining the sections was not given details of the child's age or the cause of death.

**Method of Assessment of Terminal Segment.** Our concept of the terminal respiratory unit of the lung is of that mass of air spaces distal to a terminal respiratory bronchiole, the latter being a complete tube lined by epithelium. This, in Miller's (1947) classification, consists of the alveolar duct, atria and alveoli. Several methods of assessment were tried but the only one showing adequate reproducibility consisted of ignoring all the bronchioles completely lined by epithelium and noting only those lined by epithelium in one part of the wall. From the centre of such a respiratory tube, a perpendicular line was dropped on to the nearest and definite connective tissue septum (Fig. 1). This vertical line was made by using a single hair diaphragm in the eye-piece of the microscope. The number of alveoli cut by this line was then counted. This method overcomes, as far as is possible, the effects of varying degrees of collapse or of the presence of fluid or exudate in some alveoli. Ten such counts were done from each case. It is surprising how few such measurements can be taken from any one section. After all counts had been completed the means were correlated with age on a scatter diagram. The lungs from 309 children were examined in this way.

Fig. 1, showing sections from the lungs of a child of approximately 28 weeks maturity, and from a child of 11 months, illustrates the method of counting the alveoli.

## Results

The final average figures in the different age groups, together with the errors of the means based upon the standard deviations and number of cases, are given in the Table and shown graphically in

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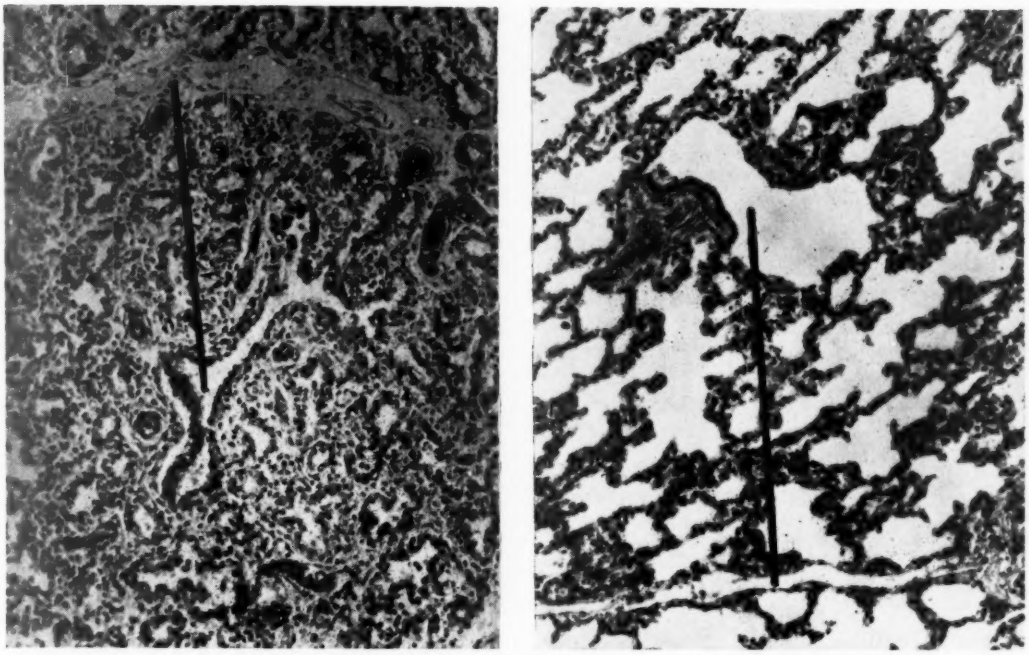

FIG. 1.—Photographs of lungs to illustrate the method of counting: one from a child of 28 weeks gestation (left) and the other from a child of 11 months (right). The black line indicates the position of the hair line as used under the microscope.

TABLE
ALVEOLAR COUNTS

| Age Group | No. of Cases | Radial Alveoli Count (mean) | S.D. | S.E. of Mean | Estimated Number of Alveoli for Terminal Lung Unit |
|---|---|---|---|---|---|
| Gestational | | | | | |
| 24–27 weeks | 6 | 2·2 | 0·60 | 0·19 | 42 |
| 28–31 weeks | 12 | 2·6 | 0·80 | 0·20 | |
| 32–35 weeks | 10 | 3·2 | 0·90 | 0·20 | 130 |
| 36–39 weeks | 9 | 3·6 | 0·90 | 0·20 | |
| Birth (40 weeks) | 25 | 4·4 | 0·90 | 0·17 | 340 |
| 1 wk–4½ mths | 38 | 5·5 | 1·38 | 0·21 | |
| 5– 9 mths | 25 | 6·6 | 1·68 | 0·34 | |
| 10–15 mths | 34 | 7·0 | 1·68 | 0·22 | 1,370 |
| 15–22 mths | 28 | 7·1 | 1·75 | 0·22 | |
| 23–30 mths | 28 | 7·2 | 1·42 | 0·19 | |
| 2 yrs 7 mths– 3 yrs 6 mths | 25 | 7·3 | 1·42 | 0·19 | 1,556 |
| 3 yrs 7 mths– 4 yrs 6 mths | 15 | 7·5 | 1·52 | 0·39 | |
| 4 yrs 7 mths– 5 yrs 6 mths | 13 | 7·6 | 1·12 | 0·31 | 1,715 |
| 5 yrs 7 mths– 6 yrs 6 mths | 8 | 7·8 | 1·31 | 0·28 | |
| 6 yrs 7 mths– 7 yrs 6 mths | 9 | 8·0 | 1·31 | 0·28 | |
| 7 yrs 7 mths– 8 yrs 6 mths | 4 | 8·2 | 1·50 | 0·28 | 2,200 |
| 8 yrs 7 mths– 9 yrs 6 mths | 5 | 8·5 | 1·70 | 0·35 | |
| 9 yrs 7 mths–10 yrs 6 mths | 6 | 8·7 | 1·80 | 0·40 | 2,630 |
| 10 yrs 7 mths–11 yrs 6 mths | 4 | 9·0 | 1·82 | 0·40 | |
| 11 yrs 7 mths–12 yrs 6 mths | 5 | 9·3 | 2·00 | 0·40 | 3,220 |

Note: Gestational age, based upon the last menstrual period, is used up to birth and postnatal age after birth.

Fig. 2. There is very great variability between children of the same age; some lungs were found from children of 2 years of age showing a similar alveolar count to that of children of 10 years. There is an increase in the alveolar count throughout the whole of childhood. The radial alveolar count goes from approximately 2·5 at 28 weeks of gestation to 4·4 at full term. By the age of 1 year, the alveolar count increases to nearly seven. This increase continues in an apparently uniform way throughout the whole of childhood, until it reaches between eight and nine at the period just preceding


FIG. 2.—Graph showing the mean and standard error of mean of the radial alveolar counts ('alveolar depth'), related to age.

puberty. Unfortunately we were unable to continue our examination into the older age group, there being no suitable material available to us.

The counts given here represent the number of acini cut by an apparent random 'radius' within the terminal respiratory unit. The latter probably varies in form but basically is a compressed sphere. If this terminal unit were a sphere, the number of alveoli in it would be given by the formula $2/3\ n^3$, i.e. approximately $2{\cdot}1\ n^3$ (where 'n' is the number of alveoli cut by the radius). If the terminal unit were a cube, 'n' would represent a half of the length of a side and the alveolar count $(2n)^3$, i.e. $8n^3$. The formula for a sphere represents the smallest theoretical number and that for the cube by no means the largest. If we take, for convenience, $4n^3$, this gives the terminal respiratory unit at full term $4 \times (4{\cdot}4)^3 = 340$ alveoli. At 1 year this becomes 1,370, and at 10 years 2,900, i.e. an apparent nine-fold increase.

## Discussion

There is now no doubt that the ideas that the lungs are fully formed by 6 months' gestation, and that the act of breathing is responsible for later difference in appearance (Barnard and Day, 1937) or that the lung is mature at birth (Norris, Kockenderfer and Tyson, 1941), are false. We have found that the terminal respiratory unit contains apparently nine times as many alveoli at the age of 10 years as at birth. This does not represent the full rate of development as this assumes that the total number of terminal units remain the same. Willson (1928) showed that in white mice there was an increase in the number of branches of the respiratory tree from 21 and 23 in the newborn to 29 and 30 in the adult and, from the study of sections from lungs of 15 children, stated that the human lung tree showed a similar increase branching after birth. Bremer (1935) working on opossum lungs suggested that the bronchioles grew distally by muscularization and epithelialization of the alveolar ducts so that what were at one time alveolar ducts, later became respiratory bronchioles. This view was also held by Broman (1923). Animals apparently vary considerably in the degrees of relative lung maturity at birth (Broman, 1923; Engel, 1953), and thus animal studies are not directly applicable to man in this respect. It has been shown quite conclusively (Cohn, 1940) that in the rat, there is an active production of new alveoli in compensative hypertrophy of a lobe in response to the removal of another lobe of the same lung. Evidence regarding alveolar growth in man is very scanty and rests largely on finding mitotic figures in the lining cells of alveoli and respiratory tubules in infants. Palmer (1936) found 17 generations of respiratory tubes in the human newborn and Broman (1923) suggested that there were six to seven further generations found after birth. This gives 131,000 ($2^{17}$) terminal respiratory units at birth and $2^{24}$,

i.e. 1,677,000 in the mature lungs (a 127-fold increase in terminal units!). We have demonstrated that there is a nine-fold postnatal increase in the number of alveoli in the terminal unit. Thus there is a theoretical overall increase of $9 \times 127 = 11{,}243$, i.e. an increase of more than 10,000-fold after birth, which is much greater than that of the circulating blood cells. It is of interest that Willson (1928) considered that the air spaces in the young child were larger than in the adult, and suggested that children were normally in a state of relative emphysema. Dubreuil, Lacoste and Raymond (1936) considered that the lung of the newborn consisted of alveolar ducts only and that all of the alveoli developed after birth.

The method of alveolar multiplication is not certain. It has been suggested that the new alveoli are formed *in utero* by the production of septa across the existing saccula (Loosli and Potter, 1951). Ham and Baldwin (1941), who worked chiefly on pigs' lungs, looked upon the lung in Macklin's concept (1936), as being a structure in a state of functional interstitial emphysema, and they considered that new alveoli were not produced by the peripheral cells, but by the splitting of the alveolar walls and the penetration of air between the beds of capillaries in a kind of progressive, controlled interstitial emphysema. The now well established presence of a lining membrane to all alveoli, does not really invalidate their concept as a thin membrane could well be ballooned into the interstitial space. Fried (1956) from a study of rabbit lungs, considered that the interstitial cells of the alveolar septa, as well as becoming the intra-alveolar phagocytes, were also capable of forming alveolar walls themselves. Krahl (1955), following up the electron-micrographic studies of the lining membranes of the alveoli made by Low (1953), took the problem of development no further than Miller (1947) or Morison (1952) in showing that the epithelium of the peripheral alveoli was less attenuated than the most central ones.

The importance of the postnatal development of alveoli will be appreciated when we consider the possibility of factors such as air pollution or repeated respiratory infections interfering with alveolar proliferation and resulting in adults with a diminished reserve of alveoli.

## Summary

A systematic and statistical study has been carried out on the lungs of children dying during the later part of gestation and through childhood up to 12 years of age.

An estimate has been made of the number of alveoli in the terminal respiratory unit and this shows a rapid increase during the first year after birth and a steady increase throughout childhood, there being apparently a nine-fold increase in the alveoli after birth.

If consideration is also given to the increased proliferation of the respiratory tree after birth, there is the possibility of a thousand-fold increase in the number of alveoli between birth and puberty.

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# CORRELATION BETWEEN BIRTH WEIGHT AND CLINICAL FINDINGS IN DIPLEGIA

BY

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Since the time of Little the role of birth injury in the aetiology of cerebral palsy has been much debated (Little, 1843; 1862). Freud and Collier believed that diplegia often had its origin in prenatal life and was less frequently the result of birth injury than was generally thought (Freud, 1897; Collier, 1899, 1924). More recently attempts have been made to classify diplegic patients into two main groups:

(1) Those who are delivered prematurely and who tend to suffer from paraplegia. This group shows, on the whole, normal intelligence and no other neurological abnormalities.

(2) Those of approximately average birth weight who show upper as well as lower limb involvement. This group tends to show mental impairment and other neurological defects (Childs and Evans, 1954; Churchill, 1958; Polani, 1958).

The birth weight distributions of patients suffering from congenital paraplegia or tri- and tetraplegia are generally found to be biphasic. It has been suggested that this provides further evidence in favour of there being two major aetiological groups of diplegic patients (Childs and Evans, 1954).

In the present study, the birth weight distribution of 200 diplegic patients was analysed and correlated with the clinical findings.

## Terminology

Diplegia is used to describe a more or less symmetrical paresis of cerebral origin, more severe in the lower limbs than in the upper. The paresis may be accompanied by hypotonia, rigidity or spasticity of the affected limbs. Patients with marked involuntary movements or ataxia were not included. The patients were placed in two categories:

(1) Paraplegics, in whom the upper limbs were functionally normal, even though minor neurological abnormalities were apparent in them.

(2) Tri- and tetraplegics in whom there was some functional involvement of one or both upper limbs (Balf and Ingram, 1955).

## Selection of Patients and Methods of Study

The series comprised 200 diplegic children referred to the Edinburgh Clinic of the Scottish Council for Care of Spastics; 58·5% were males and 41·5% females. Their ages ranged from 14 months to 13 years.

Patients may be referred to this clinic by school medical officers or general practitioners from any part of Scotland. Since many patients were sent because they were believed to be suitable candidates for a special school designed to cater for severely physically affected children of average intelligence, the series was highly preselected. At the clinic detailed histories were taken and examinations made by a neurologist, psychologist and orthopaedic surgeon. In addition to having access to the records of the clinic the parents were interviewed and patients examined personally in all but a few instances. Any patients in whom a postnatal cause for the condition was probable were excluded.

## Findings

**Birth Weights.** Birth weights were obtained in the majority of cases from hospital or nursing home records and in the remainder from questioning parents. The mean birth weight of 88 paraplegic patients was 5·1 lb. (S.D. 0·23), and of 112 tri- and tetraplegic patients was 6·1 lb. (S.D. 0·2). The frequency distribution of birth weights in both groups shows a bimodal curve (Fig. 1). The distribution of birth weights in the general population showing a unimodal curve is given for comparison. This distribution was obtained from a series of live births in an Edinburgh hospital (Drillien and Richmond, 1956), allowance then being made for infant mortality. The paraplegics show a major peak at about 4 lb. and a smaller one at 8 lb. In the tri-

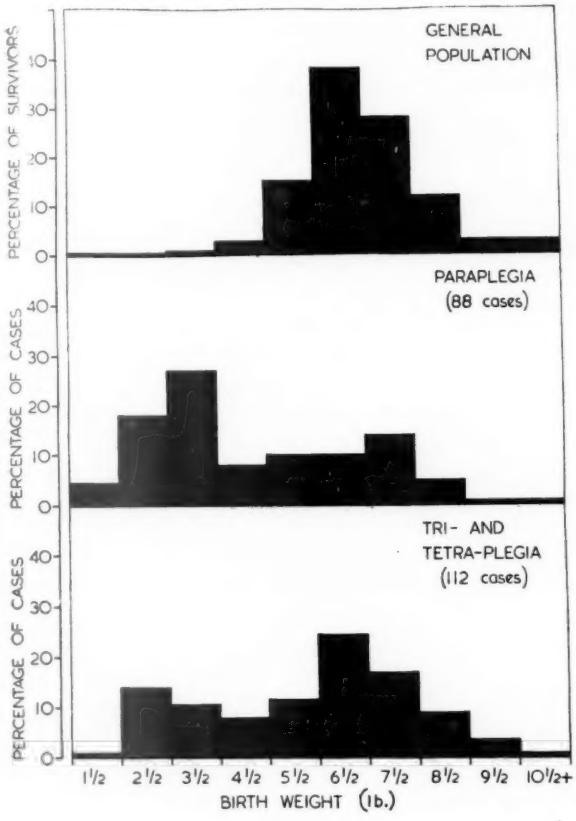


FIG. 1.—Distribution of birth weights in two groups of diplegic patients compared to the distribution in the general population.

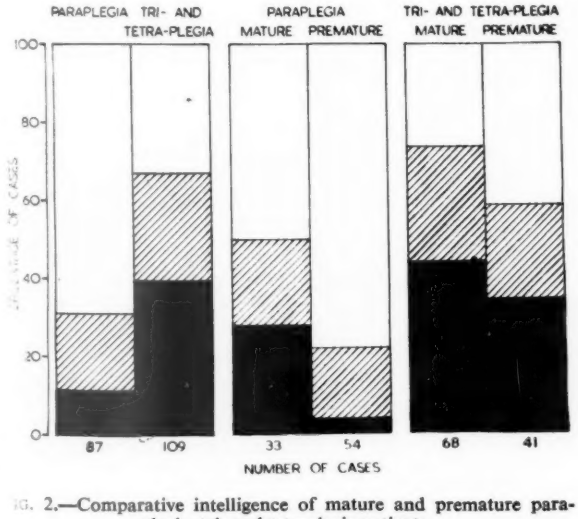


FIG. 2.—Comparative intelligence of mature and premature paraplegic, tri- and tetraplegic patients.

□ normal ▨ retarded ■ ineducable

and tetraplegic group on the other hand, the main peak is in the region of 7 lb. with a lesser rise at 3 lb. Thus paraplegic patients, as a group, tend to be premature, whereas patients with upper limb involvement tend towards average birth weights.

**Intelligence.** The intelligence of the two groups was compared on the basis of the psychologist's assessment and patients were divided into three groups:

(1) 'Normal': Those educable at a normal school or a special school catering for children of average intelligence but with physical handicaps. Arbitrarily, children with an I.Q. of 80 or above were placed in this category.

(2) 'Retarded': Those unlikely to benefit from education at schools for children of average intelligence and who were usually best placed in schools for the mentally or physically handicapped. The majority in this group have an I.Q. above 60 but below 80.

(3) 'Ineducable': Patients whom it is impossible to educate, some of whom may be suitable for training in occupation centres. An I.Q. of less than 60 forms the criterion for classifying patients in this category.

Four children, who were considered too young for an estimate of educability to be made were excluded from the analysis. From Fig. 2 and the Table it will be seen that paraplegic patients, as a group, are more intelligent than those with upper limb involvement. The difference between these two groups is highly significant statistically ($p = <0{\cdot}001$). If the patients are further subdivided into mature and premature (the criterion of prematurity being a birth weight of 5½ lb. or less), it is evident that, within each group, patients of smaller birth weight tend to be more intelligent than those of larger birth weight. However, although the difference between the mature and premature paraplegics is significant ($p = 0{\cdot}01$), there is not a statistically significant difference between the two groups of tri- and tetraplegic patients.

**Epilepsy.** The incidence of epilepsy among paraplegic patients was 9% (eight cases in 88), whereas in the tri- and tetraplegic group it was 26·8% (30 cases in 112).

**Strabismus.** No significant difference was found in the incidence of strabismus in the two groups.

As a corollary to the above findings one would expect the birth weight distribution of patients with mental defect and/or other neurological abnormalities (who are thought to represent a distinct

TABLE
INTELLIGENCE OF PARAPLEGICS AND TRI- AND TETRAPLEGICS

| Group | No. of Cases | Normal (%) | Retarded (%) | Ineducable (%) |
|---|---|---|---|---|
| Paraplegia | 87 | 68·9 | 19·6 | 11·5 |
| Matures (>5½ lb.) | 33 | 50 | 22 | 28 |
| Prematures (5½ lb. and under) | 54 | 78 | 18 | 4 |
| Tri- and Tetraplegia | 109 | 33 | 27·5 | 39·5 |
| Matures (>5½ lb.) | 68 | 26·5 | 29·4 | 44·1 |
| Prematures (5½ lb. and under) | 41 | 41·5 | 24·4 | 34·2 |

group) to show a unimodal curve. Similarly, the birth weight distribution of patients of normal intelligence who are without other neurological defects should also be unimodal (Churchill, 1958; Polani, 1959). When birth weights in these groups were analysed, the bimodality became less marked, but did not entirely disappear (Fig. 3).

The mean birth weights of the two groups differed, being 6·1 lb. (S.D. 3·1) in patients showing mental impairment and/or epilepsy and 5·0 lb. (S.D. 3·7) in the group which did not show these abnormalities.

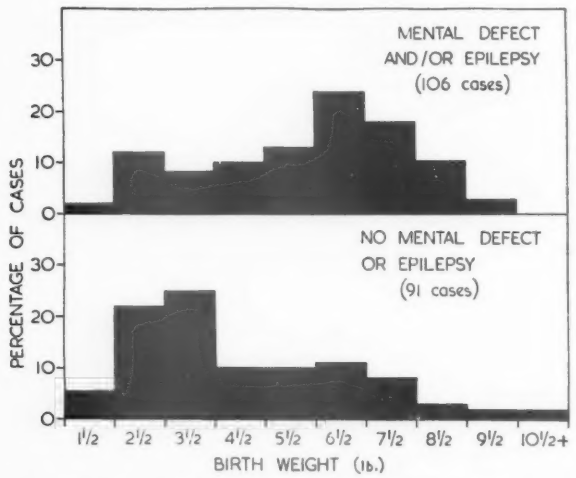


FIG. 3.—Distribution of birth weights related to presence or absence of mental defect and epilepsy.

## Discussion

When birth weights of a group of paraplegic patients and a group of tri- and tetraplegic patients were analysed the distributions in each group were bimodal. Paraplegic patients tended to be smaller at birth, more intelligent and less liable to complicating neurological abnormalities than those with upper limb involvement. Tri- and tetraplegic patients were larger at birth but more often suffered from mental retardation and epilepsy. The greater extent of their limb involvement and other clinical manifestations suggested that brain damage was more extensive than in those with paraplegia. It has been suggested that these differences in clinical findings may be correlated with differences in aetiology in the two groups. Both the premature birth and the relatively localized cerebral damage in the paraplegic patients may be the result of damaging factors operating *in utero*. Possibly the prematurity, *per se*, contributes to the cerebral palsy by depriving the nervous system of the intrauterine environment essential for its normal maturation (Polani, 1958). The more extensive cerebral involvement of the tri- and tetraplegic group may be attributed, in some cases, to birth trauma. However, even when there is a history of difficult delivery, birth trauma cannot necessarily be incriminated as foetal abnormality may have been the cause of the abnormal parturition.

## Summary

The birth weights of 88 paraplegic patients and 112 tri- and tetraplegic patients were analysed and correlated with clinical findings. Patients with paraplegia, on the whole, were found to be considerably smaller at birth, more intelligent and showed a lower incidence of epilepsy than the group of patients with upper limb involvement. The distribution of birth weights in both groups was bimodal. When the birth weights of the entire group were analysed according to the presence or absence of mental defect and epilepsy, it was found that most of the patients with mental impairment or epilepsy were of average or high birth weights and tended to show upper as well as lower limb involvement. Those who showed no other neurological abnormalities tended to be paraplegic patients of premature birth. Patients with diplegia can be segregated into two fairly well defined groups which probably differ aetiologically as well as clinically.

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# SUGARS IN THE BLOOD AND URINE OF CHILDREN FOLLOWING THE INGESTION OF DISACCHARIDES

BY

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It has previously been shown that reducing sugars are frequently excreted in the urine by mature and premature newborn babies (Haworth and McCredie, 1956; Haworth and MacDonald, 1957). Other workers, using paper chromatographic methods, have also found small amounts of sugars in the urines of children and usually higher concentrations of lactose and galactose in urines from young babies (Woolf, 1951; Apthorp, 1957; Bickel, 1959). Coant, Glowacki and Reardon (1959) found a high urinary excretion rate of sugars by premature babies which could be correlated with the amount of lactose in the feedings.

This paper describes further observations on sugars in the urine and blood of newborn babies and older children following the oral ingestion of different disaccharides.

### Analytical Methods

The chromatographic technique employed for the separation of sugars in blood and urine was the same as that used previously (Haworth and McCredie, 1956; Haworth and MacDonald, 1957), being a modification of the method originally described by Williams (1954). The filter papers were bisected after removal from the solvent and one half was sprayed with a benzidine developer and the other half with a phloroglucinol reagent (Horrocks and Manning, 1949). Glucose, fructose, lactose, galactose and pentoses were identified by the former reagent and sucrose by the latter. With a double application of the test substance, monosaccharides could be identified in concentrations of about 10 mg./100 ml. and disaccharides in rather lower concentrations.

Blood sugar estimations were performed by the method of King (1951).*

### Part I: Sugars in Urine and Blood of Mature and Premature Babies Following Ingestion of Disaccharides

**Clinical Material and Methods.** The sugars lactose, sucrose or maltose were fed to 47 newborn babies at the Women's Pavilion of the General Hospital, Winnipeg The group was unselected, except that males were preferred to females because of the greater ease of urine collection. There were 39 males and eight females. Twenty-eight of the babies were mature and 19 were premature (birth weight 5½ lb. or less). All the babies were considered healthy with the exception of two (one mature and one premature) who developed hyperbilirubinaemia which was not due to any demonstrable blood incompatibility between mother and child. Neither, however, required exchange transfusion. Five other babies developed mild 'physiological' jaundice. The birth weights of the babies varied between 3 lb. 1 oz. and 11 lb. 6 oz. and the estimated gestation of the premature babies was from 30 to 40 weeks. The ages of the babies at the time of the tests were between 1 and 23 days.

The sugars were fed in doses ranging from 0·5 to 4·2 g. per lb. at the baby's usual feeding time, i.e. three or four hours after the previous feed. In 10 instances the test sugar was given in the baby's usual feed (expressed breast milk or evaporated milk) and the additional sugar in the feed was taken into account in calculating the total dose given. In all the other experiments the sugar was given in water. The sugars were administered to several of the smaller premature babies by gavage. The dose of the sugar given was assessed approximately, allowances being made for the baby who was unable to take the total volume of fluid and for minor regurgitations. Tests were abandoned in babies who vomited.

Test tubes for urine collection were applied to the babies one hour before the test feed and specimens collected in this interval were termed 'a.c.' urines. Test tubes were reapplied at the end of the feeds and left in place until the babies voided. These specimens were the 'p.c.' urines. Some babies did not pass urine for as long as six hours after the test feed and, because it was not justifiable to withhold feedings longer than this, some 'p.c.' urines were not obtained. It was also not possible to collect the 'a.c.' urine in every instance.

Capillary blood was collected for chromatography before the test feed and one and two hours after the conclusion of the feed. In a few tests half-hour and three-hour specimens were also taken.

**Results.** Sixty-two tests were conducted on the 47 babies and the results are summarized in Tables 1 to 4.

* It has been found that this method measures 100% glucose, 85% fructose, 68% galactose and 28% lactose.

TABLE 1

SUGAR CONTENT OF A.C. URINES FROM MATURE AND PREMATURE BABIES

| | Urines Containing Sugar | Urines Containing No Sugar | Total |
|---|---|---|---|
| Mature .. .. | 5 | 20 | 25 |
| Premature .. .. | 8 | 16 | 24 |
| Totals .. .. | 13 | 36 | 49 |

URINES. Table 1 shows the sugar content of the 49 'a.c.' urines that were collected during the 62 tests. Thirteen of these urines contained one or more sugars and 36 contained no sugar. Two urines contained lactose alone, four galactose alone, five galactose and lactose, one glucose alone and one glucose and lactose. There was no statistically significant correlation between the proportions of urines which contained sugars and the maturity of the babies.

Table 2 shows the number of observations obtained by feeding lactose, sucrose and maltose and the subsequent urine sugar content. There was no statistical difference in the sugar excretion rate of the mature and premature babies. It is seen that following a feed of lactose, this sugar was found in eight of the 12 urines excreted by the mature babies and in six of 15 urines excreted by the premature babies. After sucrose feeding, three of six urines from mature babies and two of eight urines from the prematures contained sucrose. Monosaccharides were similarly found as frequently in the urines of the mature as of the premature infants. After receiving a feed of maltose, none of the 14 'p.c.' urines showed this sugar, although, nine urines contained glucose.

There was no correlation between the dose of the sugar administered and the subsequent urinary sugar content as shown in Table 3. The premature babies received on the whole higher doses than the mature babies. For instance, of 17 premature babies who received lactose on one or more occasions, eight received less than 2 g. per lb. and nine 2 or more g. per lb., while 13 mature babies received the lower dose and only one the higher.

Pentoses were found in two urines. These were not identified with certainty but may have been xylulose. Xylose was not found on any occasion in this series. The concentration in which the sugars were found in the 'p.c.' urines are expressed in Table 4. It may be seen that sugars were most commonly present in concentrations below 200 mg./100 ml., but glucose, fructose and sucrose were occasionally found in higher concentrations. A 'trace' indicates that there was a very clear but faint band on the filter paper, showing monosaccharides in a concentration of about 10 mg./100 ml. and disaccharides in a somewhat lower concentration. There was no

TABLE 2

SUGARS FOUND IN THE BLOOD AND URINE AFTER FEEDING LACTOSE, SUCROSE OR MALTOSE TO 47 NEWBORN BABIES

| | Lactose | | | Sucrose | | | Maltose | | |
|---|---|---|---|---|---|---|---|---|---|
| | Mature Babies | Premature Babies | Total | Mature Babies | Premature Babies | Total | Mature Babies | Premature Babies | Total |
| No. of Patients .. .. | 14 | 13 | 27 | 7 | 6 | 13 | 9 | 6 | 15 |
| Urines: | | | | | | | | | |
| No. of tests .. .. | 14 | 17 | 31 | 7 | 9 | 16 | 9 | 6 | 15 |
| No. examined .. .. | 12 | 15 | 27 | 6 | 8 | 14 | 9 | 5 | 14 |
| Glucose .. .. .. | 5 | 0 | 5 | 0 | 5 | 5 | 5 | 4 | 9 |
| Galactose .. .. | 6 | 11 | 17 | 0 | 0 | 0 | 0 | 0 | 0 |
| Lactose .. .. .. | 8 | 6 | 14 | 0 | 0 | 0 | 1 | 1 | 2 |
| Fructose .. .. .. | 0 | 1 | 1 | 5 | 4 | 9 | 0 | 0 | 0 |
| Sucrose .. .. .. | 0 | 0 | 0 | 3 | 2 | 5 | 0 | 0 | 0 |
| Pentose .. .. .. | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 1 |
| No sugar .. .. | 3 | 2 | 5 | 1 | 2 | 3 | 4 | 1 | 5 |
| Blood: | | | | | | | | | |
| No. of tests* .. .. | 4 | 14 | 18 | 1 | 5 | 6 | 0 | 2 | 2 |
| Glucose .. .. .. | 4 | 14 | 18 | 1 | 5 | 6 | 0 | 2 | 2 |
| Other sugars .. .. | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

* Fasting and usually one- and two-hour specimens.

TABLE 3

SUGAR CONTENT OF 'P.C.' URINES RELATED TO THE DOSE OF SUGAR ADMINISTERED

| Dose | Sugar Given | No. of Urines | No. of Urines Containing No Sugar | Disaccharide* | Monosaccharide* |
|---|---|---|---|---|---|
| <2·0 g./lb. | Lactose | 18 | 3 | 11 | 11 |
| | Sucrose | 8 | 3 | 3 | 5 |
| 2·0 g./lb. or more | Lactose | 9 | 2 | 3 | 11 |
| | Sucrose | 6 | 0 | 2 | 9 |

* Indicates the number of sugars found in the urines, i.e. several urines contained more than one sugar.

correlation between the concentration of sugar in the urine and the dose administered or the maturity of the baby. Two of the babies excreting the largest amount of sucrose were mature and had received less than 2 g. per lb. sucrose, the other was a premature who had taken more than 2 g. per lb.

The jaundiced babies behaved no differently from the other babies with respect to sugar excretion.

TABLE 4
CONCENTRATIONS OF SUGARS IN P.C. URINES

| Concentration (mg./100 ml.) | No. of Urines Containing Sugars | | | | |
|---|---|---|---|---|---|
| | Glucose | Galactose | Lactose | Fructose | Sucrose |
| Trace .. .. | 5 | 7 | 3 | — | 1 |
| <100 .. .. | 4 | 5 | 5 | — | — |
| 100–200 .. | 8 | 5 | 8 | 9 | 1 |
| >200 .. .. | 2 | — | — | 1 | 3 |
| Totals .. | 19 | 17 | 16 | 10 | 5 |

BLOODS. Bloods were chromatographed during 26 tests on 19 babies and, as shown in Table 2, no sugar other than glucose was found.

**Part II: Sugars in Urine and Blood of Older Children Following Ingestion of Disaccharides**

**Clinical Material and Methods.** The subjects were 47 in-patients in the Children's Hospital, Winnipeg, ranging in age from 5 months to 15 years. There were 24 males and 23 females. The children were carefully selected and were as 'normal' as possible. Many of the children were suffering from minor skin infections, some were in hospital for investigation of such conditions as convulsions and others were convalescent from infections such as pneumonia. None of the children had had elevated temperatures for 48 hours before the tests, none were taking drugs, such as hormones, which might have had an effect upon their metabolism and none were suffering from any metabolic disorder. Patients with gastro-intestinal disease were not included with the exception of four children who were carriers of *E. coli* or salmonella organisms. These four children had had normal bowel movements for at least one week preceding the tests and were all said to have normal appetites. They were receiving standard hospital diets but otherwise the carbohydrate intake before the tests was not controlled.

The tests were performed at 9 a.m. after the subjects had been fasted from midnight. After the fasting blood specimens had been taken the children drank the sugars dissolved in water flavoured with lemon. The dose of the sugar administered was 1 g. per lb. body weight, the minimum dose 15 g. and the maximum 50 g. Further blood specimens were initially taken half, one and two hours after the feed and in later experiments an additional quarter-hour specimen was also taken. These bloods were chromatographed and analysed for total sugar content. From eight of the children, five and 10-minute bloods were also analysed for total sugar.

Urines for chromatography were collected one hour after the test feed, but in some of the children no sample was obtainable.

Five additional 'normal' children (four males and one female) whose ages ranged from 6 weeks to 21 months were given lactose by mouth under the same conditions as detailed above. Immediately following the feed, urine collection was started and continued for eight hours. An approximate quantitative estimation by paper chromatography was made of the sugars in each of the urines.

**Results.** Eighteen children received lactose, 22 sucrose, and seven maltose.

The results of paper chromatographic analysis of the urines and blood are shown in Table 5. It can be seen that 12 of the 15 urines obtained from the 18 children who were given lactose contained sugars (lactose was present in six of them) and only three contained no sugar. In an 18-month-old girl a trace of lactose was found in the 15-, 30- and 60-minute blood samples, but not in the fasting and two-hour samples. No lactose was found in the urine of this child. In 16 urines, collected from 22 children who were given sucrose, fructose was identified in eight, five of which also contained sucrose. The remaining eight urines contained no sugar.

Sucrose and fructose were found together in the blood of four children. These were different children from the five who excreted this combination of sugars in the urine, although two of these five children showed fructose alone in the blood. Glucose was naturally also present in all the blood samples chromatographed. Maltose was not found in the blood or urine of any of the seven children who had received this sugar. A trace of glucose was present in one of the seven urines, the others contained no sugar.

The concentrations of the sugars found in the urine were all between 50 and 100 mg./100 ml. except for a 5-month-old baby who excreted approximately 120 mg. of lactose per 100 ml. The sucrose and/or fructose

TABLE 5
SUGARS IN BLOOD AND URINE AFTER FEEDING LACTOSE, SUCROSE OR MALTOSE TO 47 CHILDREN

| | Sugar Administered | | |
|---|---|---|---|
| | Lactose | Sucrose | Maltose |
| No. of patients .. .. | 18 | 22 | 7 |
| 'p.c.' Urines:* | | | |
| No. examined .. .. | 15 | 16 | 7 |
| Glucose .. .. | 1 | 1 | 1 |
| Galactose .. .. | 11 | 0 | 0 |
| Lactose .. .. .. | 6 | 0 | 0 |
| Fructose .. .. | 0 | 8 | 0 |
| Sucrose .. .. .. | 0 | 5 | 0 |
| No sugar .. .. | 3 | 8 | 6 |
| Blood: | | | |
| Glucose .. .. | 18 | 22 | 7 |
| Galactose .. .. | 0 | 0 | 0 |
| Lactose .. .. .. | 1 | 0 | 0 |
| Fructose .. .. | 0 | 6 | 0 |
| Sucrose .. .. .. | 0 | 4 | 0 |

* Figures indicate number of sugars found in the urines, i.e. several urines contained more than one sugar.

TABLE 6

AGES OF 40 CHILDREN GIVEN LACTOSE AND SUCROSE IN RELATION TO SUGARS FOUND IN BLOOD AND URINE

| Sugar Fed | Age | No. of Cases | Sugar Excreted | No Sugar Excreted | No Urine Collected | Sugar* in Blood | No Sugar* in Blood |
|---|---|---|---|---|---|---|---|
| Lactose | 5–11 mths | 5 | 2 | 1 | 2 | 0 | 5 |
| | 1–3 yrs | 6 | 4 | 1 | 1 | 1 | 5 |
| | 4–8 yrs | 3 | 2 | 1 | — | 0 | 1 |
| | >8 yrs | 4 | 4 | 0 | — | 0 | 4 |
| Sucrose | 5–11 mths | 4 | 3 | 0 | 1 | 1 | 3 |
| | 1–3 yrs | 10 | 3 | 4 | 3 | 4 | 6 |
| | 4–8 yrs | 4 | 2 | 1 | 1 | 1 | 3 |
| | >8 yrs | 4 | 0 | 3 | 1 | 0 | 4 |

* Other than glucose.

identified in the blood of six children were only present in 'trace' amounts which corresponded to concentrations of about 20 mg./100 ml.

Table 6 shows the ages of the 40 children who were given lactose and sucrose in relation to the sugars found in the urine and blood. The older children who were given lactose excreted sugars to the same degree as the younger and no relation between age and sugar excretion was demonstrated. No sugar, however, was found in the three urines obtained from the four children over the age of 8 years who were given sucrose, and no fructose or sucrose was found in their blood. The five children who excreted sucrose were all under 3 years of age. Sucrose and fructose were found in the blood of an 8-year-old boy, but unfortunately no urine specimen was obtained from this child.

Table 7 and Fig. 1 show the mean blood sugar levels following feeding the three sugars. On 18 occasions blood sugar levels were obtained 15 minutes after the test feed as shown in column 6 of Table 7 and by the separate points in Fig. 1. The 15-minute levels following the administration of lactose were higher than the 30-minute levels, but for the other two sugars the 'peak' was at 30 minutes. The differences between the 30-minute levels following the administration of sucrose (143 mg./100 ml.) and lactose (116 mg./100 ml.) are statistically significant ($p = <0{\cdot}01$). The differences between the 30-minute levels of the sucrose and maltose curves, the maltose and lactose curves, and the levels at other time intervals are not statistically significant. Five- and 10-minute blood sugar levels were also obtained in four subjects following the administration of lactose and in four following sucrose. The mean

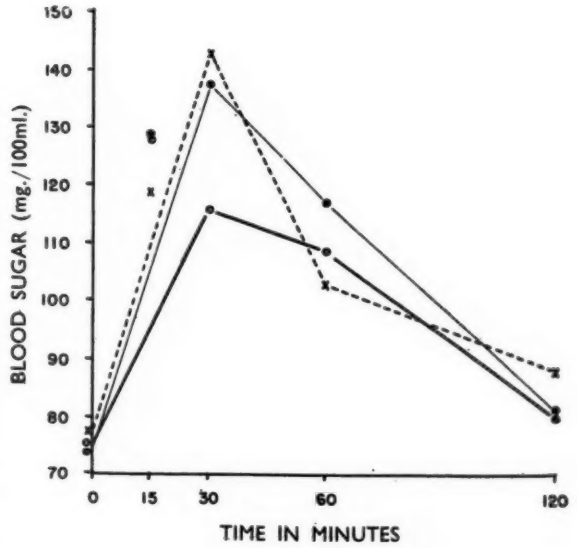


FIG. 1.—Mean blood sugar levels following the oral ingestion of lactose, sucrose and maltose (fastings 15-, 30-, 60- and 120-minute levels).

O———O mean levels after lactose, all cases (18)

× - - - - - × mean levels after sucrose, all cases (22)

●———● mean levels after maltose, all cases (7)

TABLE 7

MEAN BLOOD SUGAR LEVELS (mg./100 ml.) OF 47 CHILDREN GIVEN LACTOSE, SUCROSE AND MALTOSE BY MOUTH

| Sugar Fed | No. of Tests | Fasting | Time after Ingestion (min.) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 5 | 10 | 15 | 30 | 60 | 120 |
| Lactose | 18 | 75 | 101 (4) | 108 (4) | 128 (9) | 116 | 109 | 80 |
| Sucrose | 22 | 77 | 103 (4) | 113 (4) | 119 (6) | 143 | 103 | 88 |
| Maltose | 7 | 74 | — | — | 129 (3) | 138 | 117 | 80 |

Numbers in parenthesis indicate the number of children upon whom 5-, 10- and 15-minute estimations were obtained.

levels are shown in columns 4 and 5 of Table 7 and the mean blood sugar levels of these eight children are expressed in Fig. 2.

Table 8 shows the approximate amounts of galactose and lactose excreted over an eight-hour period by the five young children who were given lactose by mouth. It can be seen that the total amounts excreted were very small, 120 mg. of lactose in the urine of Case 3 being the largest amount found.

## Discussion

The results obtained in Part I confirm the earlier findings that sugars are frequently excreted in the urine of newborn babies (Haworth and McCredie,

TABLE 8

TOTAL AMOUNTS OF SUGAR EXCRETED OVER EIGHT HOURS BY FIVE CHILDREN FOLLOWING DOSE OF LACTOSE BY MOUTH

| Case No. | Age (mths) | Sex | Weight lb. | Weight oz. | Dose of Lactose (g.) | Volume of Urine (ml.) | Total Sugar Excreted (mg.) | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Lactose | Galactose |
| 1 | 1½ | F | 11 | 4 | 15 | 41 | 8 | 8 |
| 2 | 6 | M | 17 | 0 | 17 | 49·5 | 7·5 | 7·5 |
| 3 | 21 | M | 34 | 0 | 35 | 97 | 120 | 43 |
| 4 | ½ | M | 6 | 6 | 15 | 89 | 18 | 11 |
| 5 | 2 | M | 11 | 2 | 20 | 127 | 19 | 19 |


FIG. 2.—Mean blood sugar levels following the oral ingestion of lactose and sucrose (fastings 5-, 10-, 15-, 30-, 60- and 120-minute levels).
O———O mean levels after lactose (4 cases)
× - - - - - - × mean levels after sucrose (4 cases)

1956; Haworth and MacDonald, 1957). Part II shows that older children also frequently excrete sugars after the ingestion of sugars by mouth.

With the exception of the pentoses which were found in two newborn urines, there can be little doubt that the urinary sugars originated from the gut because there was such a close association between the sugar ingested and that subsequently found in the urine. In Part I more urines contained sugars after the sugar feed (Table 2) than those collected before the feed (Table 1). It seems likely that the galactose, glucose and lactose found in 13 of these 49 'a.c.' urines were derived from the milk feeds these babies had received three to four hours before the tests were performed. Tables 2 and 5 show that the sugar fed to the babies in Part I and the older children in Part II had a considerable influence on the type of sugar excreted in the urine. Sucrose was never found unless sucrose had been fed and galactose was never found unless lactose had been fed. In Part I lactose was found in the urine of two babies who had received maltose, but it is again likely that this was the result of preceding milk feeds. Fructose was found on one occasion after a lactose feed, but this baby's previous feed had contained sucrose.

That some lactose may escape hydrolysis in the gut and subsequently appear in the urine has been known for many years (Folin and Berglund, 1922; Winter, 1931; Koehler, Rapp and Hill, 1935). The investigations reported here show that it is a very frequent occurrence in babies and children. Although as much as 200 mg. of lactose per 100 ml. was found in the urine of some babies, Table 8 indicates that the amount of lactose excreted in the urine during an eight-hour period was only a very small fraction of the total dose given to these five babies.

Galactose, which together with glucose, is released by the hydrolysis of lactose is thought to be transported to the liver where it enters the 'glucose pool'. If the load of galactose entering the liver by the portal vein is too great for that organ to metabolize, some of the sugar will escape into the systemic circulation and because there is no renal threshold for galactose (Hartmann, McCoy, Swarm and Nakasato, 1954), it will be excreted. Rowe (1924) found that 30 g. was the maximum dose of galactose that could be ingested by adults without galactose appearing in the urine. Folin and Berglund (1922) found that the ingestion of only 10 g. could cause sugar to be excreted. Shay, Schloss and Bell (1931), on the other hand, found no correlation between the age, weight or dose given to their subjects and the subsequent amount of galactose excreted in the urine. No relation between the dose of sugar given and the urinary excretion of sugar could be demonstrated in the tests on the babies in Part I (Table 3).

Sucrosuria following the oral ingestion of sucrose has been recognized by other workers (Murschhauser,

1921; Elmer, Krasowska and Ptaszek, 1939; Lahdensuu, 1947). A dose of sucrose 2 g. per kg. body weight was considered by some to be the upper limit of tolerance. Again, no relation between the dose given and sugar excretion was demonstrated in the observations reported here. Several babies who were given more than 2 g. sucrose per lb. body weight (Table 3) and several older children who received 1 g. per lb. did not show sucrosuria. Any sucrose escaping hydrolysis in the gut is evidently treated after absorption as a foreign substance and excreted (Keith, Wakefield and Power, 1932; Keith and Power, 1937). Sucrose was identified in five of 14 urines collected from newborn babies and in five of 16 urines from older children who had received this sugar (Tables 2 and 5). Three of the babies excreted the sugar in a concentration greater than 200 mg. per 100 ml. (Table 4). Sucrosuria of such a degree, occurring in approximately a third of these children after sucrose feeding, raises doubts as to the significance of the findings of sucrosuria in the cases reported by Reiner and Weiner (1939), Owen and Lewis (1956), and the syndrome of hiatus hernia, mental defect and sucrosuria described by Moncrieff and Wilkinson (1954) and Woodruff (1958). Certainly the degree of sucrosuria exhibited by the children which these authors recorded was no more than that shown by the normal children reported here. Perry, Lippman, Walker and Shaw (1959), who recently reported findings very similar to mine, came to the same conclusion. Moncrieff and Wilkinson (1954) stated that when sucrose and lactose were given together in the diet of their patients, other sugars were excreted more easily in the urine. I have no additional observations to make about this statement except to emphasize that normal children apparently excrete sugars so frequently after sugar-containing feedings.

It is noteworthy that maltose was never found in either blood or urine following maltose feeds. This is in sharp contrast to the frequency with which the other disaccharides, lactose and sucrose, were found in the urine after feedings with these sugars. I have no satisfactory explanation to offer. It is possible that the maltase secreted by the small bowel may be more efficient than sucrase and lactase, resulting in complete hydrolysis of the maltose into its component glucose molecules. Alternatively it has been suggested that blood may contain some maltase (Long, 1947) so that any of the sugar which escapes hydrolysis in the gut may be split after absorption. It is hoped to conduct further observations upon this subject.

In view of the frequent finding of sucrose, fructose, lactose and galactose in the urines after sugar feeds it is surprising that sugars were not demonstrated more often in the blood. In fact, galactose was not observed in any of the blood samples obtained from 18 babies and 18 older children who were given lactose feeds and lactose was only found on one occasion. Sucrose was not found in the blood of any of the newborn babies who were given this sugar, although sucrosuria occurred in five (Table 2). Of 22 older children who were given sucrose, sucrose and fructose were found in the blood of four. Unfortunately urines were not collected from two of these four children, but in the urines of the other two, no sugar was found in one and fructose in the other. Of five children showing sucrosuria and fructosuria, fructose was found in the blood of two and no sugar other than glucose in the other three. It would be expected that an ingested sugar which has escaped metabolism in the body and been excreted in the urine would be demonstrable in the systemic blood. Conversely, sugar appearing in the peripheral blood should be found in the urine if the sugar is a 'non-threshold' substance which lactose, galactose and sucrose presumably are. The most likely cause for the discrepancy in the blood and urinary findings is that the chromatographic technique used was not sufficiently sensitive to demonstrate low concentrations of sugars in the blood. However, any galactose in the blood of those children who were given lactose feedings must have been present in concentrations lower than about 10 mg. per 100 ml. or it would have been detected. This is supported by the finding that only very small amounts of galactose were excreted over an eight-hour period by the five children upon whom quantitative estimations were performed (Table 8). It may be calculated that the blood levels would be less than 1 mg. per 100 ml. to give rise to this amount of galactose in the urine, assuming that galactose is a 'non-threshold' substance, even allowing for the lower renal clearance in infancy (Rubin, Bruck and Rapoport, 1949). This is in conflict with the conclusions of Hartmann, Grunwaldt and James (1953) who stated that galactose formed up to 40% of the total blood sugar in infants after milk feedings. Dormandy, Leak and Grant (1959) reached similar conclusions to those of Hartmann *et al.* (1953), although employing different analytical methods. It should be pointed out, however, that these two groups of workers only *concluded* that the bloods they examined contained large amounts of galactose because of the difference between the total sugar and the glucose. Further information has recently been obtained bearing on this subject (Haworth and Ford, 1960).

There appeared to be little correlation between the ages of the children, the dose of sugar fed to them and the subsequent frequency of sugar excretion or the concentration of the sugar in the urine. The urines from the older children, however, with one exception, contained less than 100 mg. per 100 ml. of sugar, while higher concentrations were more commonly found in the urines of the newborn babies (Table 4). This may have been because the latter babies received, on the whole, relatively higher doses of sugars than the older children, although Table 3 shows that the dose of sugar administered to the newborn babies appeared to bear no relation to sugar excretion. Sucrose was not found in any of the six urine samples obtained from children over 3 years of age, but little conclusion can be drawn from this especially since fructose and sucrose were found in the blood of an 8-year-old boy from whom, unfortunately, no urine was obtained.

Table 1 shows no significant difference in the sugar content of the urines from mature and premature babies before the test feed and Table 2 shows that premature babies excreted sugars to no greater degree than the mature babies after the sugar feed, and this in spite of the fact that on the whole they received higher doses of sugars. This is not in accord with previous findings that premature babies excreted sugars more often than mature babies (Haworth and MacDonald, 1957). Bickel (1959) also found more sugars in the urine of premature babies especially during the first 10 days of life. In retrospect there may be a valid explanation for the difference in sugar excretion rate between mature and premature babies previously found. The mature babies studied by Haworth and McCredie (1956) were fed by 'demand', and the premature babies (Haworth and MacDonald, 1957) were fed three hourly. Both groups were fed with breast milk, but it seems likely that the bigger babies may have 'demanded' feeds less often than three hourly and unfortunately no record of the times of the feeds of these babies was kept. Since the urinary sugar content has been shown to be closely related to sugar ingestion, if premature babies were fed more often than the mature, this would account for the greater number of urines containing sugar from these babies; the times of urine collection were not correlated with times of feeding.

Concerning the glycaemic response to the oral administration of lactose, sucrose and maltose in Part II (Table 7), several features are worthy of comment. Earlier workers had found that lactose ingestion caused only minimal elevation of the blood sugar (Field, 1919; Folin and Berglund, 1922; Koehler *et al.*, 1935), but these authors were handicapped by inaccurate analytical methods. Greenwald and Pennell (1930) observed that blood sugar curves in infants following the administration of lactose and sucrose closely paralleled that following glucose administration, but the curve following dextri-maltose was lower and more prolonged. The curves shown in Fig. 1 are very different from those shown by Greenwald and Pennell and reveal a rapid rise in blood sugar after the administration of the three sugars. In the case of lactose a 'peak' value 15 minutes after administration of the sugar is shown. Following sucrose and maltose the 'peak' was at 30 minutes. The shape of a blood sugar curve is to some extent dependent upon the frequency of the blood sugar estimations, and it is very possible that the true 'peaks' of the sucrose and maltose curves might have been shown to have been between 15 and 30 minutes if more frequent blood samples had been obtained. Dodds, Fairweather, Miller and Rose (1959) recently commented upon this feature and showed that the standard method of performing a glucose tolerance test, in which samples of blood taken fasting and at 30, 60, 90 and 120 minutes, may sometimes show an abnormally flat curve when in fact a more normal type of response is demonstrated if additional samples of blood are taken between 15 and 30 minutes. Table 7 and Fig. 2 show that the blood sugar level had risen by 30% in as short a time as five minutes after the ingestion of sucrose and lactose by each group of four children. Rabinowitch (1945), Rabinowitch and Mountford (1947) and Dodds *et al.* (1959) have also demonstrated the rapid rise in blood sugar following sucrose administration and it has now been shown that an equally rapid rise of blood sugar occurs after lactose ingestion. Since sugars are not absorbed to any appreciable degree from the stomach (Long, 1947) and there is no evidence that disaccharides can be hydrolysed proximal to the small bowel, it is indeed remarkable how rapidly sucrose and lactose pass into the small intestine, are hydrolysed, absorbed and reach the systemic circulation. Unfortunately, no five- and 10-minute blood samples were obtained following maltose, although 15-minute blood sugar levels following the administration of this sugar were comparable to those following sucrose and lactose.

The only statistically significant difference between the three curves shown in Fig. 1 is that the mean 30-minute blood sugar levels following sucrose administration were greater than those following lactose. This difference was common to all age

groups studied. There are two possible explanations for this difference:

1. It might be argued that because galactose stimulates the release of insulin and fructose does not (Foa, Galansino, Costa and Pozza, 1956), the galactose released into the blood after hydrolysis of lactose had a depressant action upon the blood glucose. This is a recognized phenomenon in congenital galactosaemia in which condition high blood levels of galactose occur (Isselbacher, 1959). However, it has been shown that although some galactose must reach the systemic blood because of the frequent observance of galactosuria after lactose ingestion, the amounts were undetectable by the chromatographic method used. It is difficult to imagine that these small amounts of galactose, which must be less than 10 mg. per 100 ml. would exert an appreciable hypoglycaemic effect.
2. The method of King (1951) used for measuring total blood sugar is a 'true sugar' method but not a 'true glucose' method. Fructose was observed by paper chromatography in six of the 22 30-minute blood samples obtained from those children who ingested sucrose. Smaller amounts might have been present in more. Sucrose is not a reducing sugar and is not estimated by the King method. The 'sucrose curve' would therefore, be a measure of glucose and some fructose and the 'lactose curve' of glucose alone, since, as already stated, no other sugar was detected by chromatography in these blood samples. This seems the most reasonable explanation for the difference of the 30-minute blood levels in the two curves, although it does not explain why the 'sucrose curve' was not higher than the 'lactose curve' at other time intervals. In fact, the mean 15-minute blood sugar level of the latter curve was higher than the former although the difference is not statistically significant. This question could only be solved by repeating the experiments using the glucose oxidase method so that it would be known that only glucose and no other sugar was estimated.

It must be mentioned that these blood sugar curves should not be accepted without certain reservations. The subjects were not normal children; they were hospital patients and, although they were not suffering from any generalized acute illness at the time of the test, their glycaemic response to the sugars may not have been normal. It has been shown that the glucose tolerance test is abnormal in the presence of infection, even skin infection (Schmidt, Eastland and Burns, 1934). However, it is doubtful whether this factor would have caused the observed difference between the sucrose and lactose curves because the two groups of children who received these sugars were fairly evenly matched as far as their original illnesses were concerned. It is also known that the preceding carbohydrate diet has a great effect upon the glucose tolerance test (Himsworth, 1935). The subjects were not taking a controlled diet before the tests were performed. They were, however, all eating the standard hospital diet well and it is likely that their preceding carbohydrate intake was fairly uniform.

**Summary**

Forty-seven newborn babies and 47 older children were fed with the disaccharides lactose, sucrose or maltose. Subsequent urine collection showed a high sugar excretion rate.

The source of urinary hexoses and disaccharides is undoubtedly the gut, because a sugar was not found in the urine unless a feed containing that sugar, either free or in combination, had recently been fed. Small amounts of the disaccharides, lactose and sucrose, escape hydrolysis in the gut, are absorbed unchanged and subsequently excreted in the urine.

Although earlier work had suggested that premature babies excreted sugars to a greater degree than mature babies, this was not confirmed in the present series of observations. The degree of sugar excretion did not apparently depend on the maturity or age of the child or the dose of the sugar administered by mouth.

The finding of sucrosuria in one-third of the children who were given sucrose by mouth makes it unlikely that the sucrosuria that has been described in association with mental deficiency is anything more than a coincidence.

Sucrose and/or fructose were found in the blood of six children following a feed of sucrose, but these were not the same children who excreted this combination of sugars in the urine. Lactose was found in the blood of one child following a lactose feed, but galactose was not demonstrated on any occasion. This discrepancy between blood and urinary findings was almost certainly due to technical reasons.

Maltose was not found in the blood or urine following feedings of this sugar. The reasons why this disaccharide should behave differently from lactose and sucrose have been discussed.

I wish to thank many physicians who have allowed me to examine patients under their care, and the nursing staffs of the Winnipeg Children's and General Hospitals who have helped in the collection of specimens. I am also grateful to Mr. H. Birnboim for technical assistance, Dr. R. J. Cadoret for help with the statistical evaluation and Drs. H. Medovy, B. Chown, S. Israels and K. Finkel for their advice and criticism. This work was supported by a grant from the Winnipeg Clinic Research Institute and a Mead Johnson Grant for Paediatric Research administered by the American Academy of Pediatrics.

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# ADRENAL CORTICAL HYPOPLASIA IN SIBLINGS

BY

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There have been two reports recently of adreno-cortical insufficiency in infant siblings. Mitchell and Rhaney (1959) reported it in two brothers, the first dying at 53 days and showing hypoplasia of the adrenal glands as the only apparent cause of death. The brother was born three years later, and exhibited a similar clinical picture of vomiting, wasting and dehydration shortly after birth. Biochemical studies were attempted but it became necessary to treat the child with adreno-cortical hormones and with sodium chloride added to his feeds. The child has remained alive to date, and it is assumed that he also suffers from adreno-cortical hypoplasia. Shepard, Landing and Mason (1959) reported adreno-cortical deficiency in two sisters. The first was well until 10 months and then developed a typical clinical picture. She died at 30 months and autopsy showed very small adrenal glands. There was no evidence of tuberculosis. The sister of this case, one of non-identical twins, developed symptoms after her first birthday; the other twin is healthy. After investigation, cortisone therapy was started and has had to be maintained, with much improvement. Neither sister exhibited a craving for salt and therefore the cortical deficiency is selective. This condition need not necessarily manifest itself early in childhood. The first case of Briggs, Goodwin and Wilson (1951), a boy of 12 years, had been fond of salt since infancy and clinically showed well developed Addison's disease. Radiographs showed calcification of mesenteric lymph nodes, but none in the region of the adrenal glands. Treatment with 'eucortone' at first, and later with D.C.A. pellet implants, and with sodium chloride orally, has been effective, and he was well at the time when the article was published. This boy's brother, 17 years of age, developed a more acute illness with epigastric pain, vomiting, loss of weight and increased depth of skin pigmentation. Treatment was given as for an Addisonian crisis, but he died 72 hours after admission to hospital. Necropsy revealed small adrenal glands, and histological examination showed atrophy of the cortex of each. There was no evidence of tuberculosis. The thymus was large. Both parents were healthy and the authors suggested that a genetic factor may be involved as in thyrotoxicosis, diabetes mellitus and the Laurence-Moon-Biedl syndrome.

We report a further family showing adrenal hypoplasia. Both boys in this family died in the neonatal period and received minimal corrective treatment. Therefore, the histological appearances of their endocrine glands are unaffected by therapy.

### Case Reports

In 1953, the mother became pregnant for the first time, but had a spontaneous miscarriage at 4½ months. The cases reported were the result of second and third pregnancies.

**Case 1.** This male infant was born in hospital on May 4, 1955, as a spontaneous vertex delivery at full term after a normal pregnancy. The birth weight was 7 lb. 12 oz. (3·52 kg.). 'Physiological' jaundice appeared for a few days. Before dismissal, there had been occasional vomiting after breast feeding, but the condition subsided. The baby was well for his first four days at home, and then his condition deteriorated, and he was admitted to the Royal Hospital for Sick Children, Glasgow, on May 17, 1955. On that day his motions were green and very loose.

He was dehydrated, with poor muscle tone, although he was 113% of his expected weight. Lumbar puncture gave a clear cerebrospinal fluid. Rectal swabs revealed no pathogenic organisms. Four days later his general condition was improved but he remained rather listless. On May 23, 1955, he collapsed suddenly with copious green vomitus. 'Eucortone' 0·5 ml. was given every four hours. Surgical opinion was sought, and at laparotomy a volvulus was found involving the caecum and ascending colon. This was reduced and an obstructing band was divided. 140 ml. of quarter-strength normal saline with 5% glucose was given intravenously over the next six hours. Oral fluids were started four hours postoperatively and 'eucortone' was stopped on the fifth postoperative day. His condition improved over seven postoperative days, but on the eighth day (June 1, 1955) he went off his feeds once more, became marasmic and he died on June 2, 1955, at 4 weeks of age.

At necropsy the child weighed 5 lb. 10 oz. (2·55 kg.).

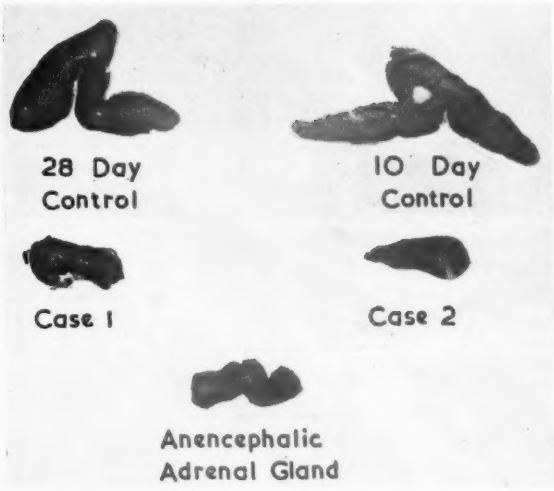


FIG. 1.—Specimens of adrenal glands of Cases 1 and 2 compared with normal controls for these ages and with an anencephalic adrenal gland. (× 5/3.)

The abdominal surgical wound was healthy. The alimentary tract, liver (120 g.), pancreas and spleen (6 g.) were normal. The respiratory passages contained terminal bile-stained inhaled vomitus and the lungs showed mild patchy collapse. The heart (17 g.), great vessels, genito-urinary and central nervous systems were normal. The ductus arteriosus was widely patent. Both adrenal glands were exceedingly small (Fig. 1) and together they weighed 0·65 g. No accessory adrenal tissue was found in the para-aortic area, pelvis or in relation to the testes which were fully descended.

The histological features will be considered later.

**Case 2.** In 1958 the mother became pregnant for the third time and suffered from no infection during this period; neither were radiographs taken. The child, a male, was born at home on October 7, 1958, and weighed 8 lb. (3·63 kg.). Progress was steady for a week, but on October 15, 1958, he vomited his feeds. On October 16 he refused his feeds and was cold, listless and grey. He continued to vomit and was admitted during the night to the Royal Hospital for Sick Children, Glasgow. His parents gave the history of a child who had died three years previously 'as a result of a twisted bowel'. Unfortunately, they were unaware of the additional condition found at necropsy, and in view of the urgency of treatment because of this present child's moribund condition, the clinicians involved did not consult the previous child's case records until later. In retrospect, this was perhaps unfortunate.

Examination, the child being 9 days old, showed him to be 95% of his expected weight, listless, grey, dehydrated and with a subnormal temperature. Lumbar puncture revealed a clear cerebrospinal fluid and the W.B.C. count was 10,800/c.mm. Blood was taken for culture, but only a contaminant grew. On the assumption that the child had an overwhelming infection, an intravenous infusion of quarter-strength normal saline with 5% glucose was set up. 100 mg. of hydrocortisone were placed in the contents of the first bottle. In addition, intramuscular hydrocortisone injections of 25 mg., and intramuscular tetracycline 25 mg. were given every six hours. The child died eight hours after admission.

At necropsy the child weighed 7 lb. 3 oz. (3·26 kg.) There was no abnormality of the respiratory passages, lungs, heart (29 g.), great vessels, the alimentary tract, liver (150 g.), pancreas, spleen (6 g.), the genito-urinary or central nervous systems. The only abnormality was the presence of unusually small adrenal glands. Together they weighed 0·9 g. (Fig. 1), and no adrenal tissue was found at any other site.

There was no family history of adrenal cortical hypofunction either in the grandparents, the parents or in their sibs.

**Histological Features.** The histological details of the two cases are similar and are considered together.

ADRENAL GLANDS. Sudanophilic material is present in the zona reticularis of the adult cortex and in individual cells of the almost completely involuted foetal zone (Fig. 2). The features are the same in both cases, and are accompanied by cytomegaly in the foetal zone. The columns of the zona fasciculata are not normal for a resting gland (Fig. 3). Fig. 4 shows that there is barely any zona glomerulosa, and the cells of the zona fasciculata show much variability in size, and in nuclear and cytoplasmic staining properties. There is no evidence of the more insidious cytolytic necrosis seen in adult cases of Addison's disease (Crooke and Russell, 1935).

FIG. 2.—

Professor T. Symington, Department of Pathology, Royal Infirmary, Glasgow, has examined one gland from each case by histological and by histochemical methods, and reports that both glands have been very active, and that he is unable to find any abnormality of function by these investigations.

Normal medullary tissue is present, but it is difficult to assess whether or not this is present in normal amount.

THE PITUITARY GLAND. The glands were normally situated in both cases. Gomori's aldehyde-fuchsin method (Gomori, 1950) shows that basophil cells are present in increased numbers in both glands (Fig. 5). This finding has been confirmed by Lieb's phosphotungstic acid haematoxylin (Lieb, 1948), and modified trichrome and P.A.S. methods. Normally, basophils are present singly or in clumps of two or three cells. Fig. 5 shows marked hyperplasia in both cases, and, if anything, a tendency to become nodular in Case 1, which survived the longer.

Thus, adrenal hypoplasia is the primary defect and not the result of pituitary hypofunction in both of these children. Conclusive evidence is obtained from histological study of the other endocrine organs.

THE THYROID GLAND. The thyroid gland in Case 2, who lived for 10 days, shows no abnormality (Fig. 6b). The gland of Case 1 who lived for four weeks, shows collapsed acini devoid of colloid (Fig. 6a), an appearance

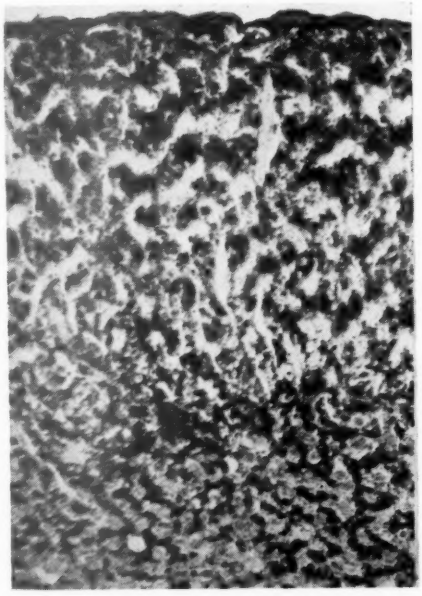

FIG. 2a.

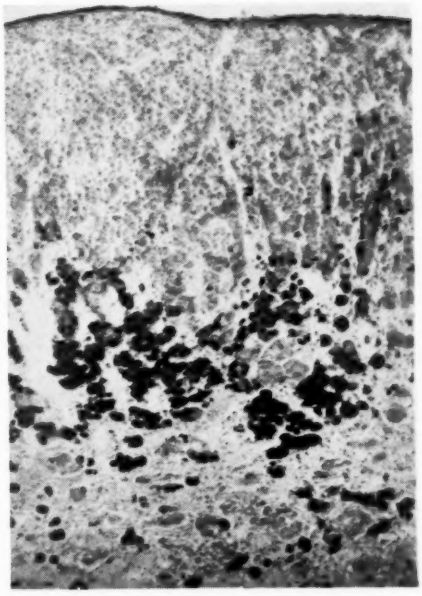

FIG. 2b.

FIG. 2.—Low power view of adrenal glands of Case 1, (a), and of Case 2, (b), stained with Sudan III and IV. The difference in quality of the two photographs is due to the gland of Case 1 being embedded in gelatin. (× 60.)

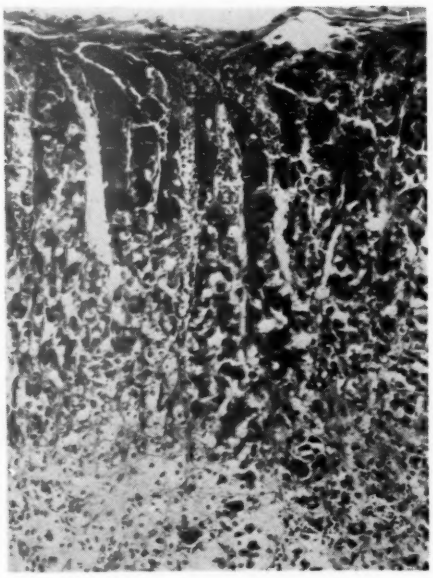

FIG. 3a.

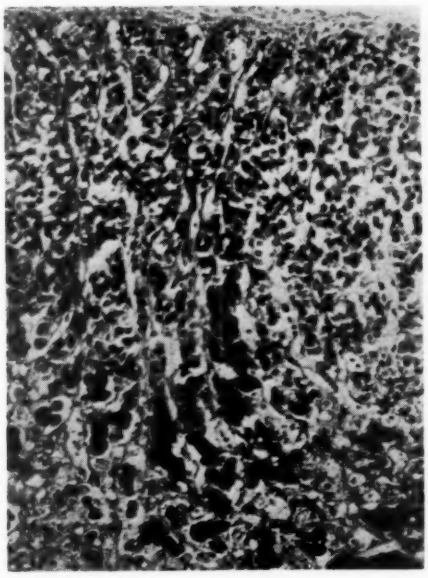

FIG. 3b.

FIG. 3.—Low power view of adrenal cortex of Case 1, (a), and of Case 2, (b), showing disorganization of cortical structure. (Masson's trichrome × 100.)

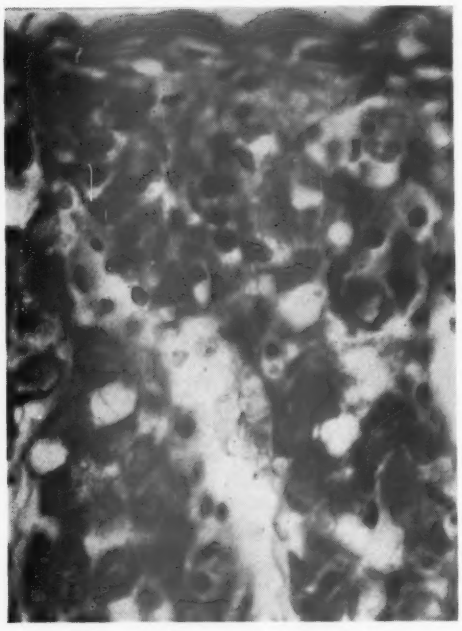

FIG. 4a.

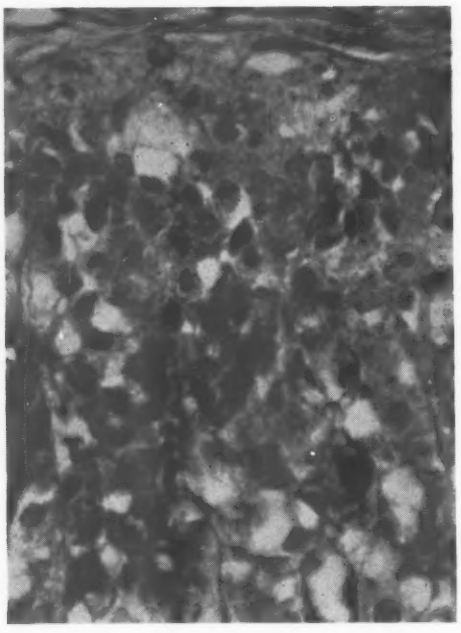

FIG. 4b.

FIG. 4.—High power view of adrenal cortex of Case 1, (a), and of Case 2, (b), showing poor zona glomerulosa and moderate pleomorphism of cells of zona fasciculata. (Masson's trichrome × 413.)

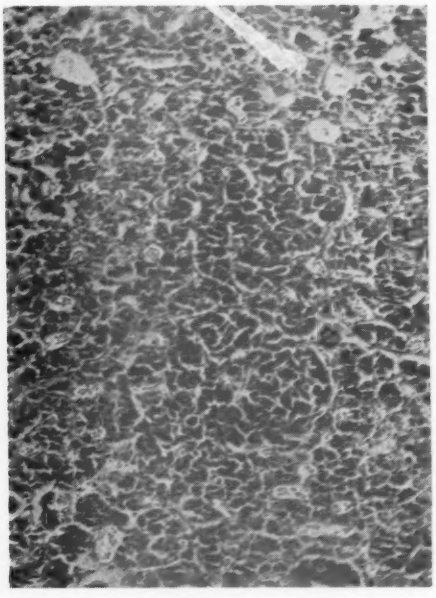

FIG. 5a.

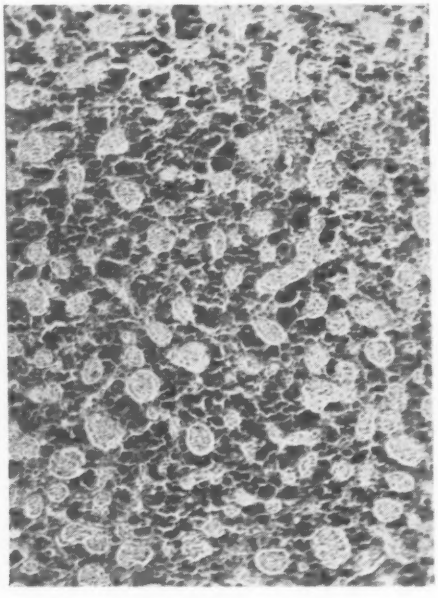

FIG. 5b.

FIG. 5.—Pituitary gland of Case 1, (a), and of Case 2, (b). The basophil cells are dark. (Gomori's aldehydefuchsin × 100.)

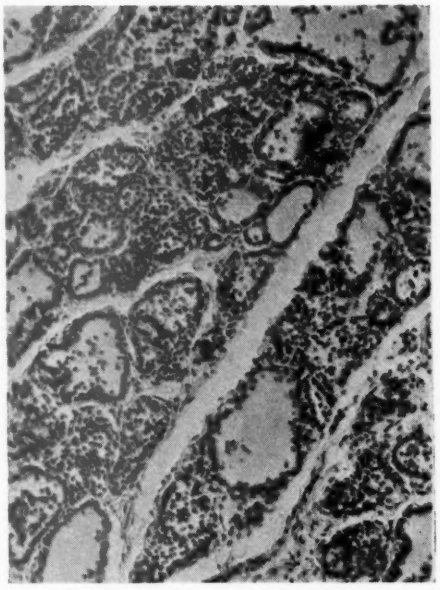

FIG. 6a.

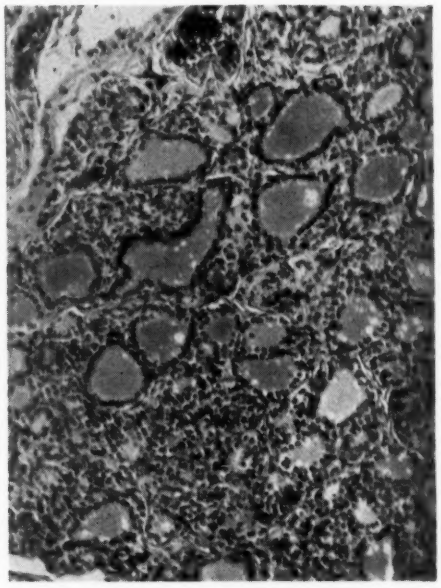

FIG. 6b.

FIG. 6.—Thyroid gland of Case 1, (a), and of Case 2, (b). The gland of Case 1 shows a thyrotrophic hormone-like effect. (Haematoxylin and Eosin × 100.)

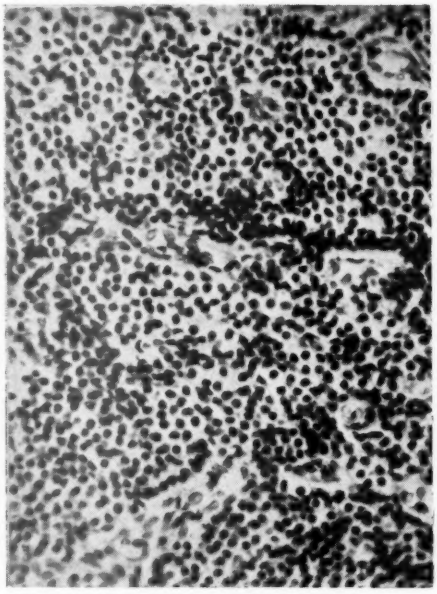

FIG. 7a.

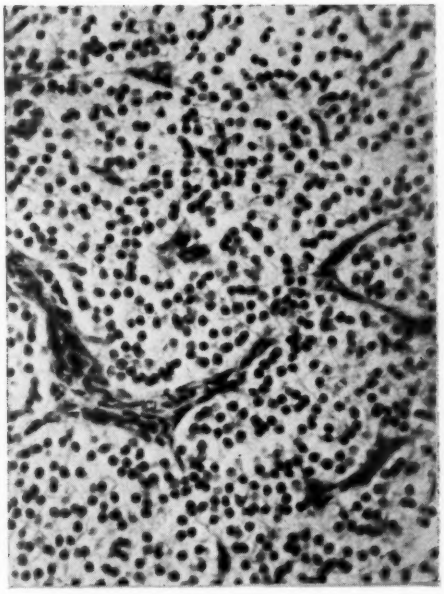

FIG. 7b.

FIG. 7.—Parathyroid gland of Case 1, (a), and of Case 2, (b). The gland of Case 1 shows some upset which is difficult to interpret. (Haematoxylin and Eosin × 100.)

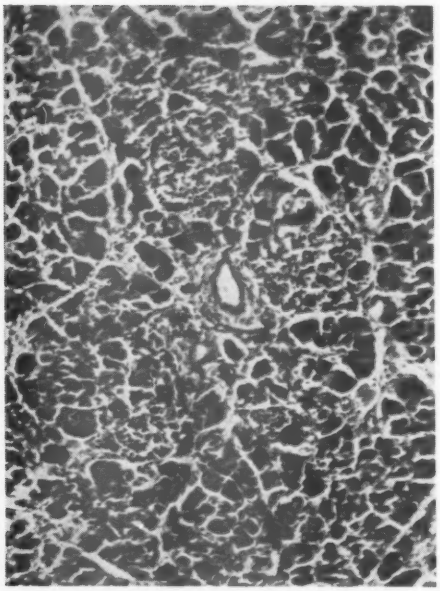

FIG. 8a.

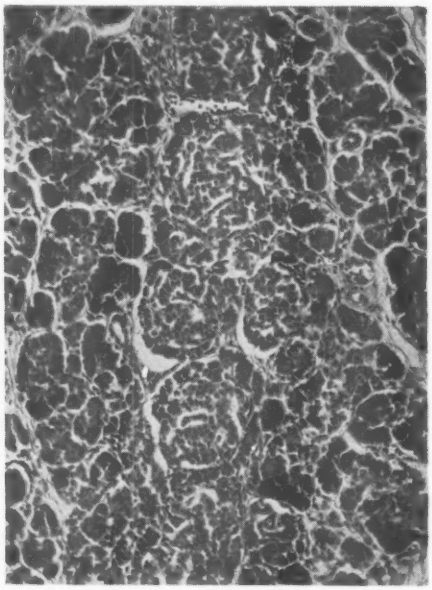

FIG. 8b.

FIG. 8.—Pancreas of Case 1, (a), and of Case 2, (b). Both are normal. (Haematoxylin and Eosin × 100.)

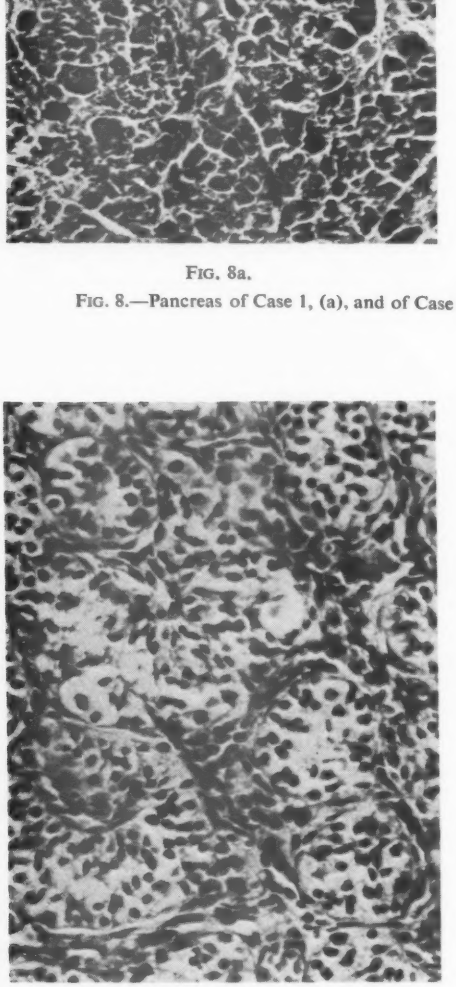

FIG. 9a.

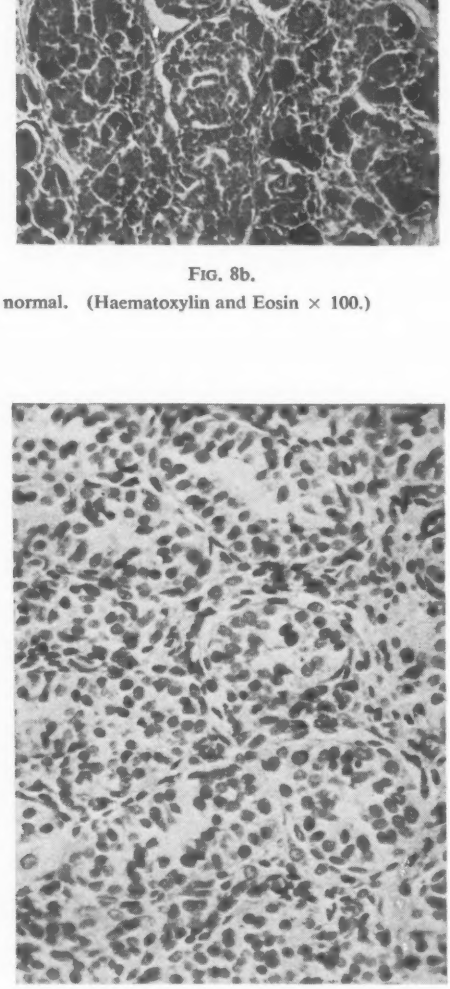

FIG. 9b.

FIG. 9.—Testis of Case 1, (a), and of Case 2, (b). The gland of Case 1 shows tubular atrophy with reduced spermatogenic activity. There is no detectable abnormality of the interstitial cells in either case. (Haematoxylin and Eosin × 100.)

which may result from over-production of thyrotrophic hormone (Sclare, 1956).

THE PARATHYROID GLANDS. In neither case do the glands appear to be unusually large or small. The gland of the shorter lived infant (Case 2) shows no histological abnormality (Fig. 7b). The gland of Case 1, however, shows an increased number of smaller cells with more hyperchromatic (or pyknotic) nuclei (Fig. 7a). We find it impossible to conclude from this whether the gland is undergoing atrophy or hyperplasia. In favour of atrophy is the apparent increase in condensation of blood vessels per field. On the other hand, Greene (1948) cites experimental evidence in favour of a parathyrotrophic hormone. Study of a section of rib from each case fails to demonstrate bone absorption, and a section of kidney from each case fails to show evidence of nephrocalcinosis by Von Kossa's stain. It may be that neither infant lived long enough to exhibit these changes.

THE ISLETS OF THE PANCREAS. Islet tissue appears to be present in normal amount (Fig. 8) and $\alpha$ and $\beta$ cells are present in both cases.

THE TESTIS. The testis of Case 2 shows a normal degree of spermatogenesis (Fig. 9b). The testis of Case 1 shows a relative degree of atrophy of the seminiferous tubules (Fig. 9a) with markedly reduced spermatogenic activity, although artefact is present as a result of unsatisfactory fixation. This finding is consistent with the records of testicular atrophy in pituitary basophilism in the adult. Interstitial cells appear to be present in normal numbers in each case.

THE THYMUS. This organ is generally considered to be an endocrine gland, although in hypofunction of the adrenal cortex it appears to behave in the same manner as lymphoid tissue elsewhere in the body (Crooke and Russell, 1935). In the present two cases, the weight of the thymus was at the upper end of the scale of normal limits, and it must be assumed that the episode of adrenal hypofunction was too acute to allow time for the glands to show hyperplasia, regeneration or a reduced rate of involution.

## Discussion

Hypoplasia of the adrenal glands is well known in association with anencephaly (Angevine, 1938) and in association occasionally with other congenital deformities of the central nervous system. In another group, however, adrenal hypoplasia is the only abnormality (Šikl, 1948; Deamer and Silver, 1950; Geppert, Spencer and Richmond, 1950; Provenzano, 1950; Welsh and Mehlin, 1954; Williams and Robinson, 1956; Harlem and Myhre, 1957; and MacMahon, Wagner and Weiner, 1957), and some of these cases have responded well to hormone therapy (e.g. Case 1 of Williams and Robinson, 1956). Some authors emphasized that the survival of these children was precarious, with sudden irrecoverable collapse if therapy were stopped even for a short period, and for this reason Mitchell and Rhaney (1959) felt that it was unjustified to investigate their second case fully while denying the infant the chance of recovery with replacement therapy. The histological appearances of the adrenal cortex of the brothers reported here resemble very closely those of Case 1 of Mitchell and Rhaney (1959) even to the presence of cytomegaly (Kampmeier, 1927; Beatty and Hawes, 1955). It should be stated that we are aware of endocrine gland involution during replacement therapy, but that we do not consider this process to be important in our cases, nor in the similar cases reviewed by us, because the adrenal glands are hyperactive. We believe that their small size is a congenital anomaly. It is essential in such cases, however, to make a thorough study of the whole endocrine system.

For example, Blizzard and Alberts (1956), Brewer (1957) and Ehrlich (1957) have described congenital aplasia or hypoplasia of the pituitary gland, and Mosier (1956) has recorded the condition, which is accompanied by hypoplasia of the adrenal glands, in siblings.

Further, our study of the literature reveals several familial syndromes which involve adrenal gland hypofunction: (1) The syndrome of hypoparathyroidism, adreno-cortical insufficiency and chronic moniliasis brought to general notice by Sutphin, Albright and McCune (1943) and followed by several reports, all from America (Leonard, 1946; Collins-Williams, 1950; Leifer and Hollander, 1953; Baker, 1954; Papadatos and Klein, 1954; Craig, Schiff and Boone, 1955; Whitaker, Landing, Esselborn and Williams, 1956; and DiGeorge and Paschkis, 1957); (2) the association of Addison's disease with thyroid gland changes in some instances (Wells, 1930; Anderson, Goudie, Gray and Timbury, 1957), and the well-known familial tendency to hyperthyroidism (Martin and Fisher, 1945), or to hypothyroidism as in sporadic non-endemic goitrous cretinism (Hutchison and McGirr, 1956), make a study of the thyroid gland essential; (3) the coincidence of diabetes mellitus and Addison's disease was described by Bloomfield (1939) and by McNicol and McNicol (1960) and since a familial tendency in diabetes is now well known, a familial tendency to both conditions simultaneously may be reported in the future; and (4) the syndrome of Addison's disease in association with familial spastic paraplegia has been recorded recently by Harris-Jones and Nixon (1955).

The existence of these conditions makes it necessary to examine not only these endocrine organs, but to examine the gonads histologically

in order to exclude the presence of ectopic adrenal tissue at this site, and also to examine the central nervous system, mainly to exclude a congenital abnormality of the fore-brain. We were unaware of the existence of the association between Addison's disease and familial spastic paraplegia and therefore a histological examination of the spinal cord was not made.

The findings suggest that our cases exhibit primary adrenal gland hypoplasia with secondary pituitary basophilism, although it is not possible to state categorically that the infants would not have developed later one or other of the syndromes referred to above, had they survived.

## Summary

Congenital adrenal hypoplasia is recorded in two brothers who died in the neonatal period.

Two previous examples of this condition in infants have been reported; one sibling has been maintained alive by replacement therapy in each.

Histological study suggests that the present two cases suffered from primary adrenal gland hypoplasia with secondary pituitary basophilism, the effects of which are demonstrable on the other endocrine glands.

We are very grateful to Dr. J. H. Hutchison for permission to abstract the case records of these two cases, to Professor S. Graham for advice, and to Professor T. Symington for studying an adrenal gland from each case.

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# POSTURAL TREATMENT OF CHILDREN WITH A PARTIAL THORACIC STOMACH ('HIATUS HERNIA')

BY

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Considerable debate centres round the best way of treating children affected with a small partial thoracic stomach ('hiatus hernia' or 'short oesophagus') uncomplicated by an oesophageal stricture. Two diametrically opposed views exist. On the one hand there are those workers who subscribe to a conservative regimen of management. Others, in the belief that the disorder is analogous to the hiatus hernia of adults, advocate surgical procedures aimed primarily at replacing and retaining the stomach wholly within the abdomen.

The following report records the long-term results achieved with conservative postural methods of treatment. The value of such therapy has been assessed by comparing the progress of treated children with the expected outcome as deduced from the natural history of the disorder (Carré, 1959). The treatment of children with a partial thoracic stomach complicated by an oesophageal stricture is not considered.

## Method

**Definition of Abnormality.** The following review is restricted to patients shown radiologically to have part of the stomach protruding through the oesophageal hiatus. In every instance the gastro-oesophageal junction has been situated within the thorax at the upper limit of the intrathoracic gastric loculus. Patients with only gastro-oesophageal incompetence have not been considered.

**Assessment of Clinical Progress.** Clinical progress has been determined objectively. The same classification of symptoms has been employed as used in the study of the natural history (Carré, 1959), namely:

*Frequent:* If vomiting and/or difficulty in swallowing solid food was noted to occur daily or at least on alternate days in children taking a normal diet for age. The routine use of a mashed diet occasioned by a child's difficulty in swallowing solids has been interpreted as implying the existence of frequent symptoms despite the fact that the child on its mashed diet might have been having little or no vomiting or dysphagia.

*Moderate:* If vomiting and/or difficulty in swallowing solid food was noted to occur on an average of less than three times weekly but at least monthly in a child taking a normal diet for age.

*Minimal:* If vomiting and/or dysphagia were absent or occurred on average less than once a month in a child taking a normal diet for age.

**Type of Patient Considered.** In the study of the natural history (Carré, 1959) it was concluded that untreated clinically affected patients could be divided into the following relatively distinct clinical groups:

| Group | Change in Symptomatology on Weaning to Mixed Diet | Prognosis | Clinically Affected Patients (%) |
|---|---|---|---|
| I | No symptoms or improved | Benign course. Majority free of symptoms by 2 years: | 60-65 |
| Survivors II | No improvement or worse | (*a*) Prolonged clinical course with 'moderate' or 'frequent' vomiting and / or dysphagia commonly persisting to at least 4 years of age; no oesophageal stricture; | 30 |
| | | (*b*) Symptomatology and progress dependent on presence of an oesophageal stricture | 5 |
| Deaths | | In the absence of an oesophageal stricture death likely to occur during infancy from combination of marasmus, biochemical disturbances and infection | <5 |

Because of the naturally occurring variation in clinical progress exhibited by individual patients, consideration of results has been restricted to the following two groups of patients whose progress in the absence of treatment could be forecast reliably.

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GROUP A. All patients in whom a partial thoracic stomach had been radiologically confirmed by 3 months of age were included. Since clinically affected children progress in a similar manner during the early weeks of life irrespective of the eventual outcome (Carré, 1957), it is apparent that all clinical types would be correctly represented in such a group. Thus, in the absence of beneficial treatment about one-third of these patients would be likely to pursue a protracted clinical course (Groups IIa and b of Natural History Study: Carré, 1959).

GROUP B. This group comprised patients who were between 6 months and 2 years of age when started on postural treatment and who were not improved clinically when weaned on to a solid diet; no patient had a proven oesophageal stricture when first seen. (Group II patients of Natural History Study: Carré, 1959.) In the absence of beneficial therapy almost all these children could therefore expect to suffer from troublesome symptoms until at least 4 years of age with about one in six developing an oesophageal stricture.

### Group A Patients

During the period of study all infant patients whose partial thoracic stomach had been radiologically confirmed by 3 months of age were treated routinely by posture from the time of diagnosis; none of these patients received any form of surgical treatment before the age of 3½ years. In view of the therapeutic policy adopted this group therefore represents a consecutive and unselected series of patients all of whom were started on postural treatment within the first 3 months of life. All surviving patients have been followed up to at least 4 years of age.

Although some patients had oesophageal narrowing on fluoroscopy, none had a proven oesophageal stricture at the time of starting treatment. All suffered from symptoms of 'frequent' severity when started on treatment. No child showed signs of a commencing spontaneous symptomatic improvement.

**Patients given 'Adequate' Postural Therapy.** In this section only those patients have been considered whose treatment fulfilled the following requirements: (*a*) Patients were kept in a sitting posture with the trunk inclined at 60° or more with the horizontal. Posturing of a lesser degree occasionally employed during the early stages of this study was found to be therapeutically ineffective (Fig. 1). As it was impossible to maintain this degree of propping

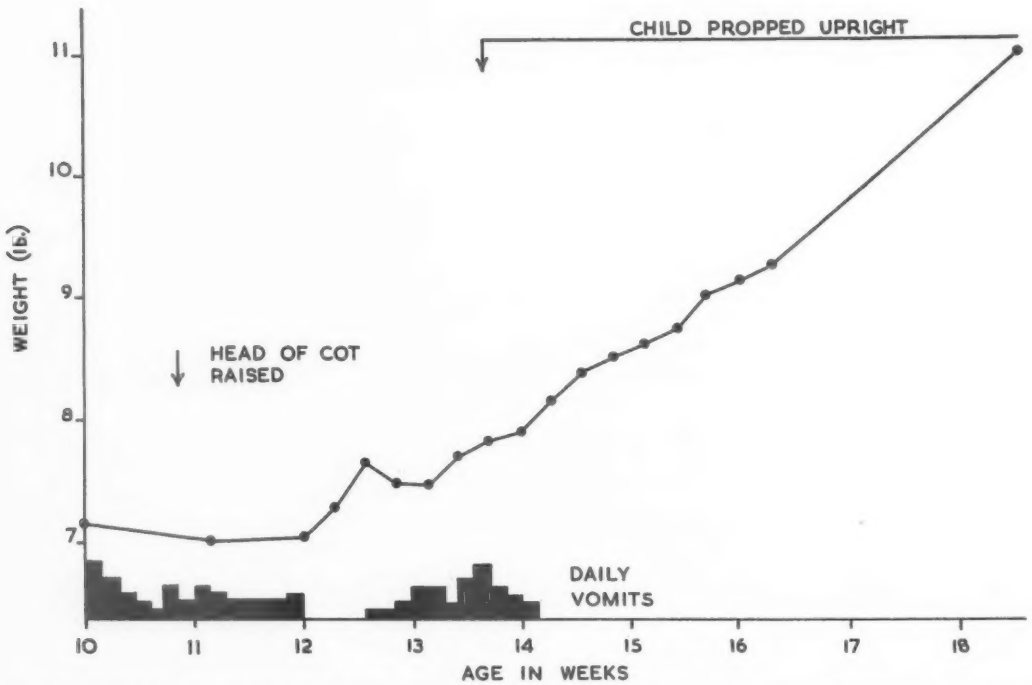


FIG. 1.—At 10 weeks this infant weighed only 10 oz. more than his birth weight. The patient was treated by propping with one pillow and raising the head of the cot on 10-in. blocks. No significant improvement was noted over a period of three weeks. Subsequent to nursing in an erect posture vomiting ceased and a rapid gain in weight was recorded. This patient was 7½ years old when last seen. There had been no recurrence of vomiting.

TABLE 1

PROGRESS OF 34 PATIENTS STARTED ON 'ADEQUATE' POSTURAL TREATMENT BEFORE 3 MONTHS OF AGE

| Case No. | 'Adequate' Postural Treatment | | Supplementary Treatment | Clinical Progress | | | Age at Last Review | |
|---|---|---|---|---|---|---|---|---|
| | | | | Severity of Symptoms and Age | | | | |
| | Age Started (weeks) | Age Discontinued (months) | | Frequent | Moderate | Minimal | Yrs | Mths |
| 16 | 1 | 12 | — | B – 1w | — | 1w –LR | 7 | 5 |
| 80* | 7 | 30 | — | B –LR | — | — | 6 | 8 |
| 81 | 2 | 10 | — | B – 2w | — | 2w–LR | 7 | 0 |
| 83 | 2 | 14 | Thickened feeds | B – 2w | — | 2w–LR | 6 | 5 |
| 87 | 12 | 12 | Thickened feeds | 5w– 4½m | — | 4½m–LR | 5 | 6 |
| 88 | 2 | 8 | — | B – 4w | 4w– 7w | 7w–LR | 4 | 0 |
| 90 | 6 | 9 | — | B – 6w | — | 6w–LR | 5 | 9 |
| 91 | 2 | 7 | Alkali | B – 2w | 2w– 5m | 5m–LR | 6 | 7 |
| 97 | 2 | 20 | — | B – 2w | 2w– 8w | 8w–LR | 7 | 1 |
| 98 | 12 | 12 | — | B – 3m | 3m– 4m | 4m–LR | 7 | 6 |
| 99 | 2 | 8 | — | B – 2w | 2w– 6w | 6w–LR | 4 | 11 |
| 102 | 2 | 14 | — | B – 2w | 2w–12m | 12m–LR | 5 | 6 |
| 103 | 3 | 4 | — | B – 3w | 3w– 5w | 5w–LR | 6 | 1 |
| 106† | 2 | 18 | Atropine, alkali | B – 3m | 3m– 4y | — | | |
| | | | | 4y – LR | — | — | 7 | 1 |
| 112 | 10 | 7 | — | B – 5m | — | 5m–LR | 6 | 3 |
| 113 | 2 | 6 | — | B – 2w | 2w– 4w | 4w–LR | 4 | 0 |
| 114 | 6 | 21 | — | B – 6w | 6w– 5m | 5m–8m | | |
| | | | | | 8m–12m | 12m–LR | 6 | 5 |
| 115 | 3 | 16 | — | B – 3w | — | 3w–LR | 5 | 10 |
| 121 | 2 | 15 | — | B – 2w | 2w– 4w | 4w–LR | 6 | 0 |
| 123 | 4 | 12 | Alkali, thickened feeds | B – 2m | 2m– 5m | 5m–LR | 5 | 11 |
| 124 | 9 days | 3 | — | B – 2w | 2w– 6w | 6w–LR | 4 | 5 |
| 126 | 7 | 16 | Thickened feeds | B – 8w | — | 8w–LR | 6 | 0 |
| 127 | 12 | 23 | Thickened feeds<br>Alkali, atropine | B – 6m | 6m–13m | 13m–LR | 7 | 4 |
| 139 | 9 days | 2 | — | B – 2w | — | 2w–LR | 5 | 3 |
| 144 | 9 days | 6 | — | B – 2w | — | 2w–LR | 5 | 1 |
| 146 | 12 | 24 | Thickened feeds | B – 5m | 5m–20m | 20m–LR | 5 | 4 |
| 147 | 2 | 6 | — | 1w– 3w | 3w– 3m | 3m–LR | 4 | 5 |
| 148 | 4 | 6 | — | B – 5w | 5w– 3m | 3m–LR | 5 | 0 |
| 149 | 12 | 14 | — | 1w–14w | — | 14w–LR | 5 | 3 |
| 154 | 3 | 9 | — | B – 6w | 6w–12w | 12w–LR | 4 | 9 |
| 156 | 2 | 12 | — | B – 4w | 4w– 9m | 9m–LR | 4 | 7 |
| 158 | 7 | 5 | — | 5w– 9w | 9w– 3m | 3m–LR | 4 | 1 |
| 159 | 4 | 10 | Thickened feeds, atropine | B – 7m | 7m– 8m | 8m–LR | 4 | 1 |
| 168 | 1 | 8 | Thickened feeds | B – 3w | 3w– 7w | 7w–LR | 5 | 3 |

* Only two vomits per year from 2 years, but food finely cut up because of dysphagia.

† Developed an oesophageal stricture; surgical repair of 'hiatus hernia' when 6 years old.

Abbreviations: d = days w = weeks m = months y = years LR = last review B = birth

without the use of some form of chair or supportive harness only those infants have been included who were kept propped up by means of some such appliance.* (*b*) Posturing was maintained continuously day and night up to the age of 1 year, or if symptoms had subsided before, until a minimum of six weeks complete freedom of symptoms had been recorded.

**Treatment Given in Addition to Posture.** The routine policy throughout was first to try the effect of posture without altering the feeding regimen in any way. If progress was considered unsatisfactory postural treatment was augmented by thickening the feeds.† In fact, only eight of 34 infants were given thickened feeds in addition to postural therapy. Treatment was further supplemented in two of these eight by the administration of alkali which was also prescribed for two others in the group.

**Results.** Thirty-four infants were treated by adequate sustained posture as defined above. All were kept under regular out-patient supervision at a special follow-up clinic throughout the period of treatment. The clinical progress of these infants is summarized in Table 1.

* Initially many methods were devised, but the plaster chair described by Hill (1953) has been used routinely in the treatment of patients during the latter part of this study. Other postural appliances have been described by Davies (1952) and Rosenweig (1954).

† *Methods used to thicken feeds:*
(i) Benger's Food—one teaspoonful to 2 oz. of milk feed.
(ii) Cornflour—one tablespoonful to a pint of milk feed.
(iii) Carob-seed flour, marketed under the name of 'nestargel' by the Nestlé Company—half to one teaspoonful to 12 oz. of feed (0·5-1% of powder to each feed).
These thickened feeds were given by feeding bottle using a teat with a large hole. Additional thickening, if desired, was obtained by merely increasing the concentration of the thickening agent.

Only four of these 34 infants suffered from either 'moderate' or 'frequent' symptoms beyond 12 months and only two beyond 2 years of age. One of these latter children (Case 80) had vomited only two to three times a year from 2 years of age until last seen when 6 years 8 months old. During this period, however, she had continued to have difficulty with swallowing and required to have solid food finely cut up. Examination by barium swallow and fluoroscopy at her last attendance showed no evidence of oesophageal narrowing. The other child (Case 106) showed no improvement with treatment and developed an oesophageal stricture. A surgical repair of the 'hiatus hernia' when she was 6 years old did not produce any significant benefit and when seen one year later she still complained of frequent dysphagia and vomiting.

These results compare favourably with the expected outcome of a similar group of untreated patients (Carré, 1959). Without treatment, it is probable that at 12 months of age about 22 and at 2 years about 15 patients would have been troubled with symptoms of either 'moderate' or 'frequent' severity. Of these, 11 would still have been vomiting more than once a month on average at 4 years with one or two having developed an oesophageal stricture. One other patient might have died in infancy.

The speed of response to treatment was variable. In some patients improvement was dramatic while symptoms in others abated only slowly over a period of months. The speed of response may be determined from the time interval between the institution of therapy and the onset of symptoms of 'minimal' severity. This period was less than two weeks in 12 patients. In a further 12 this interval varied between two weeks and three months. In eight patients the response to treatment was gradual with intervals varying from three to 17 months between the commencement of treatment and the onset of 'minimal' symptoms. Two patients failed to respond. Confirmatory observations were recorded in 20 other similarly treated patients excluded from the present review because of an inadequate follow-up. Seven of these 20 patients had virtually ceased vomiting within two weeks and another eight within three months of starting treatment. The prompt beneficial response which may follow the institution of postural treatment is illustrated by Case 121 (Fig. 2).

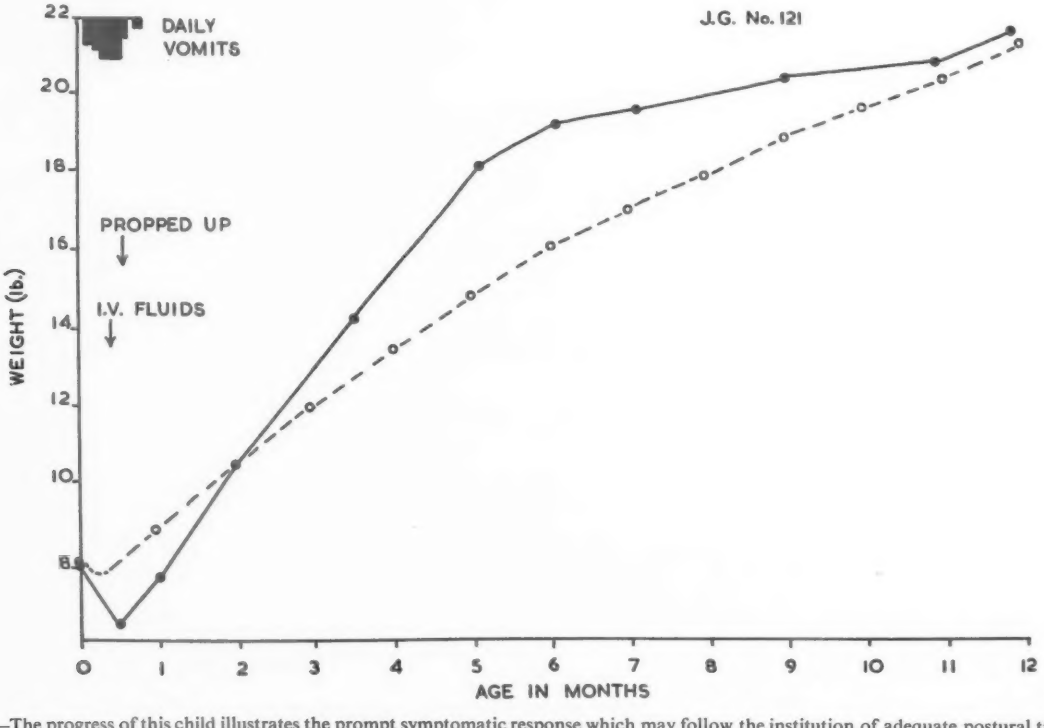


FIG. 2.—The progress of this child illustrates the prompt symptomatic response which may follow the institution of adequate postural treatment in early infancy. This infant commenced vomiting at 3 days. When 2 weeks old she weighed 1 lb. 12 oz. less than her birth weight. Following rehydration with intravenous fluids and treatment by nursing in an erect posture vomiting ceased dramatically and concurrently her weight rose steadily. She was last seen at 6 years of age; there had been no recurrence of symptoms, but she still had a demonstrable partial thoracic stomach when examined by barium swallow and fluoroscopy. Weight ————; expected weight gain - - - - - -

TABLE 2

PROGRESS OF 15 PATIENTS DIAGNOSED BEFORE 3 MONTHS OF AGE BUT GIVEN 'INADEQUATE' POSTURAL TREATMENT

| Case No. | Postural Treatment | | Supplementary Treatment | Clinical Progress | | | Age at Last Review | Remarks |
|---|---|---|---|---|---|---|---|---|
| | Age Started (weeks) | Age Discontinued (months) | | Severity of Symptoms and Age | | | | |
| | | | | Frequent | Moderate | Minimal | Yrs Mths | |
| 21 | 2 | 5 | Thickened feeds | 2d – 4 m | 4 m–11 m | 11 m–LR | 7 5 | Propped with pillows only |
| 24 | 8 | 3 | Thickened feeds | B –4½ m | — | — | 4½ m (died) | Propped for ½ hour after feeds |
| 25 | 6 | 2 | — | B –10 w | — | — | 10 w (died) | Adequately propped for ½ hour after feeds |
| 92 | 6<br>14 mths | 7<br>24 | Thickened feeds, alkali, atropine | 4 w– 8 m<br>12 m–3 y 7 m | 8 m–12 m<br>— | 3 y 7 m–LR | 4 2 | Pneumonia 11 and 19 mths; adequate propping 6 wks–7 mths; one pillow only used 14 mths–2 yrs; resection of oesophageal stricture and partial gastrectomy at 3 yrs 7 mths |
| 107 | 8 | 8 | Thickened feeds | B – 3 m | 3 m–15 m | 15 m–LR | 6 7 | Two pillows only |
| 111 | 2 | 1 | Atropine | B – 3w | 3 w– 8 w | 8 w–LR | 7 4 | Adequately postured 2–4 wks only |
| 122 | 11 | 20 | Alkali, thickened feeds | B – 6 m | 6 m–LR | — | 6 3 | Propped with pillows only |
| 130 | 6 | 30 | — | 7 d– 5 m | 5 m–17 m | 17 m–LR | 6 1 | One pillow and head of cot raised |
| 140 | 2 | 3 | Atropine, thickened feeds | B – 8 w<br>4 m– 7 m | 8 w– 4 m<br>7 m–12 m | 12 m–LR | 5 3 | Adequately propped, but for insufficient period |
| 143 | 9 | 9 | — | — | B – 4 m | 4 m–LR | 5 0 | Pillows only |
| 145 | 2 | 9 | — | B – 3 w | — | 3 w–LR | 4 6 | Adequately propped 2–4 wks only, then one pillow to 9 mths |
| 150 | 6 | 5 | — | 2 w– 6 w | 6 w–3½ y | 3½ y–LR | 4 5 | Propping adequate, but for insufficient period |
| 153 | 1 | 24 | — | B – 4 m | 4 m–2½ y | 2½ y–LR | 4 5 | Head of cot raised and one pillow |
| 164 | 6 | 18 | — | 2 w– 5 m | 5 m–12 m | 12 m–LR | 4 0 | Adequate propping 6–12 wks only |
| 165 | 12 | 12 | Thickened feeds, alkali | B –12 m | 12 m– 3 y | 3 y–LR | 4 3 | Pillows only and for one hour after meals |

Abbreviations as in Table 1.

**Patients Given 'Inadequate' Postural Treatment.** For the purpose of comparison a summary is included of the progress of 15 children given 'inadequate' treatment. Postural treatment has been judged as 'inadequate' for the following reasons. Pillows only were used to posture seven patients, while in eight instances propping though adequate in degree, was either employed intermittently or continued for an insufficient period (Table 2).

There was an additional important difference between the two groups. These patients, in contrast to those already discussed, were not kept under regular out-patient supervision. In other respects they were exactly comparable to those considered in the previous section with the exception that one patient (Case 143) had symptoms of only 'moderate' severity at the time of commencing treatment.

**Results.** Eight children were well by 2 years. Two patients died in early infancy. One child developed an oesophageal stricture. The remaining four children suffered from symptoms of 'moderate' severity beyond 2 years of age; one of these still had 'moderate' symptoms at 4 years.

These results are not dissimilar to the expected outcome should none of these children have been treated by posture. For, in the absence of treatment eight or nine would probably have been well by 2 years of age. Of the others, possibly one might have died and another developed an oesophageal stricture. The remaining four or five children would probably have suffered from symptoms of at least 'moderate' severity up to 4 years of age and longer.

### Group B

The greater strength and activity of these older patients made it infinitely less practical to effect a comparable degree of sustained propping as quoted for Group A patients. It has been necessary, therefore, to adopt much less strict criteria of treatment. Patients have been included where a genuine attempt had been made to keep them propped throughout the night and during daytime rest periods.

Children considered in this survey have been treated by posture for either a minimum period of nine months, or a period extending for six weeks beyond the onset of 'minimal' symptoms should

this have occurred before nine months treatment had been given.

No child was subjected to any surgical procedure other than oesophagoscopy during the nine months of postural treatment.

All patients considered were 4 years of age or more at the time of their last review.

**Results.** There were only nine patients whose symptomatology and treatment conformed with the above conditions. Alkali was given as supplementary treatment to five patients; two of these were given atropine as well. The clinical progress of these patients is summarized in Table 3.

Three patients developed an oesophageal stricture; one other child suffered from symptoms of 'moderate' severity until the age of 6 years 11 months. The remaining five children had only 'minimal' symptoms at 4 years of age; in four 'minimal' symptoms had dated from 2 years or younger. If untreated it is probable that only one or two of the nine patients would have shown much improvement by 4 years of age.

The response to treatment appeared to be unrelated to the age of commencing treatment. Of four whose treatment started before 12 months of age, two developed an oesophageal stricture while two were well at 4 years; of five commencing treatment between 12 and 24 months, one developed a stricture, one suffered from 'moderate' symptoms until almost 7 years and three were clinically well at 4 years.

Fig. 3 shows the progress of one patient who responded to conservative therapy.

### Complications of Postural Treatment

The only complications observed which could in any way be attributed to postural therapy were occasional sore buttocks, usually encountered at the start of treatment, and a flattening of the head similar to that described by Craig (1953).

**Flattening of Head.** The following brief review was undertaken with the object of determining more precisely the relationship of a flattened head to postural treatment. In the absence of anatomical measurements a child has been regarded as having a 'flat' head if the alteration in head shape was sufficiently obvious to cause comment. Three groups of patient are considered:

1. Children who were kept sitting up at 60° or more throughout each 24 hours for a minimum period of one month and who were followed-up for at least six months from the start of treatment.
2. Children who were postured either intermittently or for less than one month, or in whom the degree of propping was less than that stated for Group 1.
3. Patients given no postural treatment and who were between 6 months and 2 years of age when seen.

As shown in Table 4 a flattened head was only

TABLE 3

PROGRESS OF NINE PATIENTS BETWEEN 6 AND 24 MONTHS WHEN STARTED ON POSTURAL THERAPY

| Case No. | Age of Starting Postural Treatment (months) | Supplementary Treatment | Clinical Progress: Severity of Symptoms and Age | | | Age at Last Review | | Remarks |
|---|---|---|---|---|---|---|---|---|
| | | | Frequent | Moderate | Minimal | Yrs | Mths | |
| 55 | 20 | — | B–20 m<br>2 y 10 m–3 y 6 m | 20 m–22 m<br>3 y 6 m–6 y 11 m | 22 m–2 y 10 m<br>6 y 11 m–LR | 8 | 4 | Postural treatment discontinued 2½ yrs; recommenced 3 yrs 4 mths (two pillows) until 6 yrs |
| 62 | 17 | Alkali, atropine | B–12 m | 12 m–17 m | 17 m–LR | 4 | 0 | Propping discontinued 2½ yrs |
| 79 | 8½ | Alkali | B–8½ m | 8½ m–18 m | 18 m–LR | 7 | 6 | Propping discontinued 3½ yrs |
| 86 | 18 | Alkali | 9 m–18 m | 18 m–20 m | 20 m–LR | 4 | 1 | Propping discontinued 2½ yrs |
| 101 | 18 | — | B–LR | — | — | 4 | 9 | Propped 18 mths–2½ yrs; oesophageal stricture 2 yrs; repair of 'hiatus hernia' at 4 yrs 7 mths; good immediate symptomatic response |
| 110 | 6 | Alkali, atropine | B–18 m | 18 m–2 y 4 m | 2 y 4 m–LR | 4 | 3 | Propping discontinued 2 yrs |
| 119 | 10 | — | B–LR | — | — | 5 | 3 | Propping discontinued 2 yrs; oesophageal stricture 21 mths |
| 129 | 8 | Alkali | B–18 m<br>18½ m–3 y 6 m | 18 m–18½ m<br>— | —<br>3 y 6 m–LR | 4 | 1 | Treated by posture for 10 mths<br>Oesophageal stricture 16 mths; repair of 'hiatus hernia' 18 mths; no improvement; resection of stricture and oesophago-gastrostomy 3½ yrs; improved; died 4 yrs 1 mth from neuroblastoma |
| 160 | 14 | — | B–18 m | 18 m–2 y | 2 y–LR | 4 | 4 | Postured for 12 mths |

Abbreviations as in Table 1.

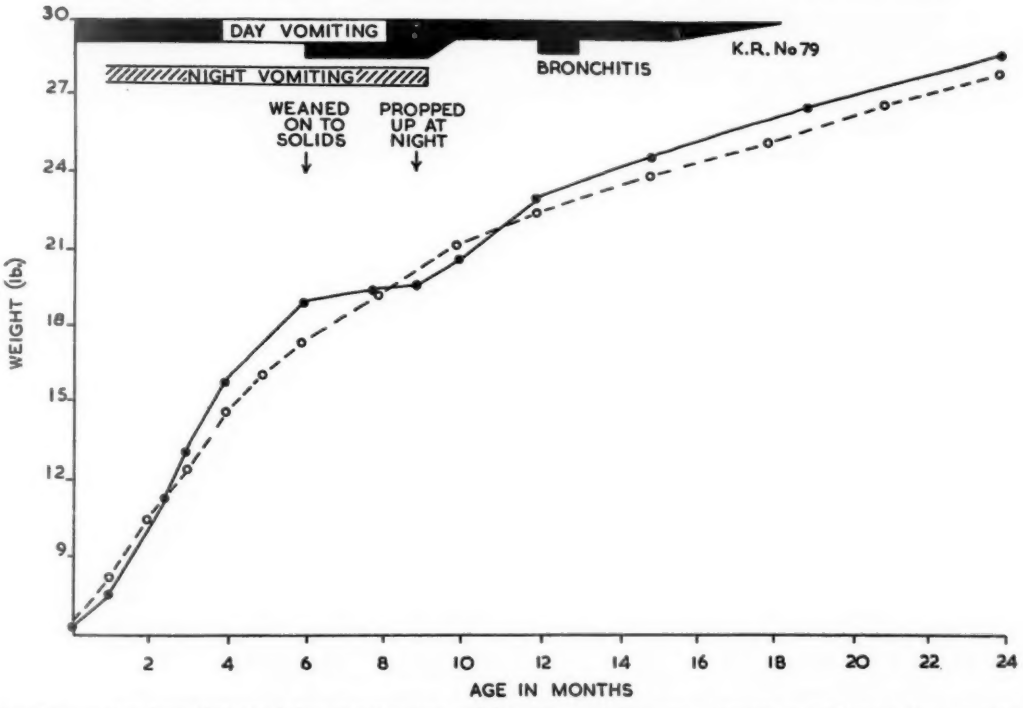


FIG. 3.—Despite vomiting from birth this infant gained weight satisfactorily until 6 months. During the following three months vomiting increased and no weight gain was recorded. No solid food was retained. From the time of starting postural treatment at 8½ months, vomiting at night, which had been a notable feature, ceased and dysphagia and day vomiting gradually subsided over a period of nine months. Except for an occasional vomit associated with respiratory infections this child remained free of symptoms up to his last review at 7½ years.

noted among children of Group 1; all were less than 3 months old when started on treatment. Eight of the 13 children who developed a 'flat' head were girls. Birth weights ranged from 4 lb. 14 oz. to 9 lb. 4 oz. with an average of 6 lb. 15 oz. Two children were noted as having developed a 'flat' head within one month of starting treatment.

## Discussion

**Value and Limitations of Postural Therapy.** Postural treatment for the purpose of this review has been regarded as 'adequate' only if it entailed keeping infants propped at 60° or more throughout the 24 hours. These requirements were originally formulated largely on the basis of theoretical reasoning during the early stages of this study in 1951.

By 1950 the aetiological importance of gastro-oesophageal reflux in the development of oesophagitis, ulceration and ultimately stricture formation in adult patients had been established (Tileston, 1906; Winkelstein, 1935; Dick and Hurst, 1942; Johnstone, 1943; Allison, Johnstone and Royce, 1943). Similar oesophageal changes noted in some children with a partial thoracic stomach appeared to have an identical aetiology as free gastro-oesophageal reflux was a frequently associated radiological feature. The damaging effect of gastric juice, hydrochloric acid and pepsin on the oesophageal mucosa had been demonstrated experimentally by Friedenwald, Feldman and Zinn (1928), Selye (1938) and Ferguson, Sanchez-Palomera, Sako, Clatworthy, Toon and Wangensteen (1950). There was, therefore, good evidence for supposing that the greatest danger to patients with gastro-oesophageal incompetence lay in the regurgitation of unbuffered and undiluted gastric juice.

TABLE 4

RELATIONSHIP OF POSTURAL TREATMENT TO ALTERATIONS IN SHAPE OF HEAD

| Age on Starting Postural Treatment (months) | Number of Patients | | |
|---|---|---|---|
| | Group 1 | Group 2 | Group 3 |
| 0–1 | 31 (7) | 6 (0) | 11 (0) |
| 1–2 | 11 (3) 49 (13) | 6 (0) 15 (0) | |
| 2–3 | 7 (2) | 3 (0) | |
| >3 | 22 (0) | 12 (0) | |

Figures in brackets indicate number of patients with a 'flat' head. For definition of groups 1, 2 and 3, see text.

Lelong, Aimé, Aubin and Bernard (1939) reported that infants with a 'brachyoesophage' were improved if nursed propped up after feeds. These observations were later confirmed by Wyllie and Field (1946), Nicod (1948) and Roviralta (1949). It seemed logical to postulate that the assumption of an erect posture by invoking the aid of gravity lessened the amount of gastro-oesophageal reflux in these infants which secondarily resulted in an amelioration of symptoms. On the basis of this reasoning it seemed particularly important that any such posturing should not be confined to short periods during the day or after feeds, but should be maintained throughout the night when the protective effect of food in buffering and diluting gastric contents was non-operative. Continued posturing throughout the 24 hours was therefore adopted as an essential requisite of 'adequate' therapy.

In addition to keeping patients propped up throughout the 24 hours, it soon became apparent that to be therapeutically effective posturing had to be of such a degree that patients were maintained in a sitting position (Fig. 1). It was found impossible to maintain this degree of propping without the use of some form of supportive harness or chair and for this reason postural treatment which did not include the use of some such appliance has been regarded as 'inadequate.'

No evidence has been obtained from this study favouring a relaxation of these measures. On the contrary, the results achieved have demonstrated that prolonged sustained propping in a sitting posture is essential if maximum benefit is to be obtained from this form of therapy. Whereas encouraging long-term results were recorded in the group of infants started on 'adequate' treatment by 3 months of age, a second comparable group given 'inadequate' therapy compared unfavourably. In fact, the ultimate prognosis of these latter children did not appear to have been materially influenced by therapy. These results also emphasize the importance of out-patient supervision. There is little doubt that an important factor contributing to the adequacy of treatment in the former group was the fact that patients were kept under regular out-patient observation. Though difficult of accurate evaluation, two features appeared to affect adversely the long-term response to treatment, namely maternal inadequacy, often aggravated by poor social conditions, and recurrent upper respiratory tract infections causing temporary exacerbations of vomiting.

It is possible to define two distinct clinical groups among infant patients based on their response to postural therapy. Of patients started on 'adequate' sustained postural treatment by 3 months of age approximately two-thirds had virtually ceased vomiting within three months of starting treatment. By contrast, improvement in the remaining one-third was slow with troublesome symptoms persisting for many months. The relative proportions of these two groups, namely two-thirds and one-third, are identical to those of the two clinical categories recognizable among untreated infant patients, i.e. Groups I and II of the natural history study (Carré, 1959). This similarity in distribution suggests that the patients who responded promptly to treatment were in fact precisely those who, if untreated, would have undergone a spontaneous clinical cure by 2 years of age (Group I). Whereas, those whose improvement was slow and protracted were probably patients who, in the absence of treatment, would have suffered from troublesome symptoms to 4 years and older, with a few developing an oesophageal stricture as a complication (Groups IIa and b). Yet, with prolonged postural therapy eight of the 10 latter patients became virtually symptom free by 2 years of age; vomiting in four of these did not cease until after nine months of continuous therapy. The absence of a rapid symptomatic response should not be interpreted therefore as an indication *per se* for abandoning postural treatment.

Postural treatment when first started in late infancy or early childhood was not accompanied by such encouraging results as noted when treatment was started during the first months of life. Nevertheless, it seems that about half of the older patients are likely to benefit from postural treatment. There are two probable reasons why treatment should be less effective when first instituted at this age. The pathological changes in the lower oesophagus are more likely to be irreversible and, secondly, sustained adequate posturing is more difficult to achieve because of these patients' greater activity and strength.

Having regard to the recorded results and analytical precautions adopted, it is concluded that postural treatment is of considerable value in the management of infants with a partial thoracic stomach uncomplicated by an oesophageal stricture. To be maximally effective, however, treatment must be commenced as early in infancy as possible, and patients should be propped at 60° or more throughout the 24 hours. Treatment should be continued for as long as 12 months should troublesome symptoms persist; in refractory cases little additional benefit is likely to result from more prolonged treatment. In those patients who respond it is advisable to continue with treatment for a further

six weeks after the virtual cessation of all symptoms.

It must be appreciated that the effectiveness of postural treatment in this study has been determined solely by reference to clinical disturbances. Although of undoubted clinical benefit, there is no evidence that postural treatment influences the radiological 'cure' rate (Carré and Astley, 1960).

Postural treatment can only be regarded as routinely applicable if at the same time it can be asserted that no permanent undesirable ill effects are likely to accrue. Craig (1953) has recorded a flattening of the head in two infants with a 'hiatus hernia' treated by posture—an observation subsequently confirmed by Davies (1953). Thirteen similar instances have been noted among 98 patients treated by posture. All 13 children who developed a 'flat' head had been started on treatment before the age of 3 months and had been maintained continuously in a sitting posture for at least one month. These latter patients represented about one-quarter of the children so treated (Table 4). Not a single instance was seen among children treated by intermittent or lesser degrees of propping, among children over 3 months of age when started on treatment nor among untreated patients. The relationship of a 'flat' head to postural therapy is further emphasized by the findings in two sets of identical twins. One set was started on 'adequate' postural treatment at 10 days of age; both infants developed a 'flat' head. Of the other set of twins one infant was treated by posture from 7 weeks; the other received no postural treatment. The twin treated by posture developed a 'flat' head, whereas the other did not.

It might be thought that the skull of a premature baby would be softer and more malleable than that of a full-term infant and that as a result premature babies would be particularly liable to develop alterations in head shape. However, it was not possible to demonstrate any relationship between birth weight and the development of a 'flat' head in this series.

It is apparent that the 'flat' head seen in certain children with a partial thoracic stomach arises secondarily to the maintenance of an erect posture during the early months of infancy. That this abnormality may develop relatively quickly is illustrated by the two patients in this series who had developed a 'flat' head within one month of starting treatment. As these 'flat' headed children grow older the alteration in head shape becomes progressively less noticeable and it is probable, though not certain, that the abnormality eventually resolves completely.

That the propping up of small babies might result in eventual maldevelopment of the spine is often of justifiable concern to parents, and Braid (1953) has questioned whether prolonged treatment in an erect position might not interfere with normal pelvic growth. Though specifically looked for, no evidence of either spinal or pelvic maldevelopment has been noted among children in this series.

The introduction of thickened feeds was of great supplementary value in the few infants slow to respond to posture alone. Alkali and atropine derivatives were given so infrequently and sporadically that no reliable assessment of their therapeutic value is possible on the basis of this study. That these agents may have contributed to the symptomatic recovery of the few patients given these medicaments cannot be discounted. It may possibly be of significance that three of the four children whose treatment first started between 6 and 24 months of age and who either developed an oesophageal stricture or were still troubled with vomiting at 4 years of age had not been given alkali. On the other hand, of the five comparable patients whose symptoms at 4 years were 'minimal', four had been given alkali as supplementary treatment. In any case, until such time as unequivocal evidence to the contrary has been produced there seems to be, on at least theoretical reasoning, sufficient justification for the use of alkali as supplementary therapy.

**Comparison of Published Results.** Although only sufficient experience has been gained from this study to justify conclusions on the value and limitations of postural therapy, the published results of both medical and surgical treatment are briefly reviewed for the purpose of comparison. Only information relating to the treatment of children with a proven partial thoracic stomach uncomplicated by an oesophageal stricture is considered. Unfortunately, a strict comparison of published results with those of this study is largely impossible because of the frequent omission of essential data on methods and duration of treatment, length of follow-up, criteria of assessment and even more important the age and type of child treated. Moreover, most reported series include both medically and surgically treated patients. This raises an additional difficulty as it is seldom clear why patients were chosen to receive either one or other form of therapy. Because of the inevitable selection involved the results quoted in such reports need to be evaluated with considerable caution.

Good clinical results following conservative postural treatment have been claimed by Lelong, Aimé and Aubin (1941), Roviralta (1952), Fox and

Hunter (1954), Swyer (1955) and Burke (1959). Unfortunately, the information provided is insufficient to permit of comparison with the observations of this study. A very limited comparison has been possible with the observations of Masse and Bader (1957). For the most part patients seen by these authors were first treated conservatively and only if the immediate response to treatment was poor were they then subjected to operation. Analysis of their results shows that of children with a gastro-oesophageal abnormality corresponding to the partial thoracic stomach of this study, 38 started on a similar medical regimen of treatment within the first three months of life; 22 (58%) responded sufficiently promptly for operative treatment to be withheld (Masse, 1959, personal communication). These observations agree with those of the present review in which it was noted that among 54 comparable patients 35% became virtually symptom-free within two weeks and 72% within three months of starting postural therapy.

In contrast, unsatisfactory results from medical treatment are quoted by Forshall (1955) and Thomsen (1955). A critical evaluation of the information provided by these authors suggests how such a contrary opinion to that of this study has come about.

On the basis of experience gained in treating nine patients by postural methods Forshall (1955) expresses disagreement with the suggestion that many ultimately do well with conservative therapy. Details of the postural methods and duration of treatment are not stated nor is the patient's age on starting treatment. However, it would appear that at least five of the nine children were over 2 years of age and two had an oesophageal stricture. As illustrated in this study such patients represent precisely those who would not be expected, and indeed do not, respond well to medical treatment. It is important that these limited observations should be viewed in their correct perspective. Referring as they do to a particular type of patient it is clear that they should not be interpreted as representative of the results of medical treatment as applied to all children with a partial thoracic stomach.

Analysis of Thomsen's (1955) data shows that 24 patients were treated by postural methods for varying periods. The use of a harness or chair is not mentioned and it is probable that the degree of propping was less than that used in the present study. Two patients died from causes unrelated to the gastro-oesophageal abnormality. Of the remaining 22 only 12 were considered to have made a satisfactory response to conservative treatment. Eleven were diagnosed before 3 months of age and, although by no means certain, it is assumed that their treatment will have dated from the time of diagnosis. With postural treatment as defined and applied in the present study 10 or possibly all would have been expected to respond. In fact only six became symptom free; their ages at the time of their last review varied from 15 months to 4 years. The other five children were considered to have failed to respond to treatment and were subjected to operation. However, consideration of the histories of these five patients indicates that in three at least postural treatment was maintained for less than six weeks. Had treatment been continued longer it is likely that these patients would also have responded. For, of comparable patients studied in this review about one-quarter showed little improvement until after three months continuous propping. The remaining 11 conservatively treated children in Thomsen's series were over 3 months of age when started on treatment. Such a group will include a high proportion of relatively severely affected children only about one half of whom are likely to respond to conservative measures. In fact, six of the 11 improved and became symptom free. Thus, although at first sight the results quoted by this author appear less satisfactory closer scrutiny reveals no significant difference from those of the present study.

A similar divergence of opinion exists with regard to the value of surgical treatment. Forshall (1955) records in a short follow-up review that surgical repair of the 'hiatus hernia' resulted in relief of symptoms in 29 of 30 children so treated. These are excellent results, but before giving credit to the surgical procedures employed it would be of considerable moment to know the age of these children at operation and, in view of its undoubted beneficial effect, to know if postural treatment was used to any extent either before or after operation. In any case a final assessment must await a more prolonged follow-up because of the possibility of relapse months after apparent surgical cure. In view of the therapeutic policy advocated by this author of 'operation in all cases in which the cardia is above the diaphragm' it can be assumed that most patients would have been operated on shortly after establishing the diagnosis, in which case the majority are likely to have been small infants. Should this in fact be so then the symptomatic results achieved are not notably different from those obtained in this review. Unfortunately, Forshall's encouraging results are not confirmed by other workers. Husfeldt (1953), for example, refers to the results of surgical treatment as being 'far from satisfactory'. Excluding three patients with an

associated oesophageal stricture only 10 of 24 patients were regarded by this author as cured following a surgical repair of the 'hiatus hernia'. Allowing for differing techniques, why should this surgeon's experience differ from that of the previous author? One important factor would seem to be the type of patient treated. In Husfeldt's series about half were over 2 years of age and there is little doubt that many had irreversible pathological changes in the oesophagus. It is noteworthy that of comparable patients treated by posture in the present study about half were similarly benefited.

Relatively disappointing surgical results have also been published by Guichard, Verger and Humeau (1956), Bettex and Genton (1957) and Robb (1957).

Doubt regarding the efficacy of surgical treatment is expressed by Burke (1959) in a follow-up report on the series of patients originally reported by Waterston (1954). Of 64 surgically treated patients only 12 responded immediately with cessation of vomiting. Of the others 'improvement had sometimes begun before surgery was undertaken, but more often it was not evident until months or even years afterwards'. It should be noted, however, that 25 children in this series had an oesophageal stricture at the time of operation.

One other report dealing with the surgical treatment is that of Duhamel (1957). Excluding patients with an oesophageal stricture, 24 of this surgeon's patients had a gastro-oesophageal abnormality corresponding to the partial thoracic stomach of this study. An excellent or satisfactory response to therapy was noted in 20; four showed no improvement. Some degree of comparison is possible with the experience recorded in the present study. It is probable that most of the patients operated on had had a trial period of medical treatment beforehand in view of the therapeutic policy adopted by this author's medical colleagues (Masse and Bader). On the evidence of the present review the nine infants who were less than 6 months old when operated on by Duhamel would probably have improved over a period of months had postural treatment been continued. In fact, following operation two of the nine responded promptly, six made a slow recovery with gradual cessation of vomiting and one was not improved. These surgical results are not therefore significantly dissimilar to what would probably have occurred had postural treatment been more prolonged. On the other hand, of 15 children operated on when over 6 months of age seven made a prompt recovery, five improved slowly and three showed little clinical change. Assuming that all had troublesome symptoms at the time of operation these results reflect an improvement on those of the present study for of comparable patients only about half benefited from prolonged postural therapy.

Although considerable experience in treating children with a partial thoracic stomach has been gained during the past few years, there exists no unanimity of opinion on the relative value of therapeutic procedures. In a disorder such as the partial thoracic stomach where there is such a wide variation in the naturally occurring clinical progress of individual patients it is imperative that strict analytical precautions should be adopted when assessing the value of therapeutic measures. Failure to do this and a lack of appreciation of the natural history have been mainly responsible for the controversial views expressed. For this reason the present study is considered to have an important subsidiary value. It is suggested that similar analytical procedures might usefully be adopted by other workers when assessing the results of either conservative or surgical treatment. If this were done there seems good reason to expect that many of the divergent views at present expressed would soon be resolved.

**Summary**

In this study the value and limitations of postural treatment in the management of children with a partial thoracic stomach uncomplicated by an oesophageal stricture have been assessed. The clinical progress of treated patients has been compared with the expected outcome as determined from a previous study of the natural history. All patients considered were followed-up to at least 4 years of age.

It is concluded that postural treatment is of great value in the management of these patients. To obtain maximum benefit it is necessary, however, that patients be sat up at 60° or more throughout the 24 hours. This degree of propping can only be maintained by using some form of supportive harness or chair. Treatment should be continued for up to 12 months should troublesome symptoms persist.

The most favourable clinical results were recorded in patients aged less than 3 months when started on treatment; 30 of 34 so treated were virtually symptom free at 1 year of age. On the other hand, only about one half of the older patients improved.

As supplementary treatment, thickened feeds were found to be of unquestionable benefit. The value of alkali could not be accurately ascertained though the available evidence suggests that this therapy is also helpful.

The only significant complication of treatment was the development of a 'flat' head in a few patients.

This alteration in head shape was confined to children who were started on treatment when under 3 months of age and maintained continuously in a sitting posture for at least one month.

A review of the literature is included showing that although much data have been collected during the past few years there still exists no unanimity of opinion and much confusion of thought on the relative merits of different therapeutic procedures. It is submitted that a failure to employ strict analytical methods when assessing the value of therapy combined with a lack of appreciation of the natural history have been the factors mainly responsible for the controversial views expressed.

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# 'SWEAT TEST' RESULTS IN NORMAL PERSONS OF DIFFERENT AGES COMPARED WITH FAMILIES WITH FIBROCYSTIC DISEASE OF THE PANCREAS

BY

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Many workers have confirmed the original observation of Darling, Di Sant'Agnese, Perera and Andersen (1953) that sweat sodium and chloride levels in children with fibrocystic disease of the pancreas are three to four times higher than those found in normal children. The reason for this has not yet been defined, but the difference is so clear in children that the 'sweat test' has become one of considerable diagnostic value.

However, the normal variation of sweat sodium and chloride levels in adults and in persons of varying age from childhood into adolescence and adult life has not been so clearly defined. Despite the absence of sound data of this type there is an increasing volume of literature in which the authors interpret small variations in these levels as an indication of abnormality in the groups of persons concerned. For instance, Di Sant'Agnese, Darling, Perera and Shea (1953) and Smoller and Hsia (1959) state that a proportion of parents and siblings of children with fibrocystic disease of the pancreas have somewhat raised sodium and chloride levels and that this indicates their carrier or heterozygous state; Hsia, Driscoll, Greenberg, Lee and Lanoff (1958) state that patients with allergies, particularly asthma, show higher levels than other children; Wood, Fishman, Reemtsma, Barker and Di Sant' Agnese (1959) state that some adult patients with chronic chest disease such as chronic obstructive pulmonary emphysema show raised levels and should be considered 'formes frustes' of fibrocystic disease of the pancreas.

Earlier work (Anderson and Freeman, 1958), in which a small group of parents and siblings were compared each with a group of normal adults and children failed to show any difference between the sweat sodium and chloride levels in the corresponding groups, but it did indicate that the levels in adults tended to be higher than those in children. This work has been extended to include groups of greater numbers, primarily to delineate the sweat sodium and chloride levels throughout life. These levels have then been compared at the corresponding ages with those obtained in larger groups of parents and siblings of patients with fibrocystic disease. The levels in children with chronic or recurrent chest disease, including asthma, have also been compared with those of children of similar ages free from chest illnesses.

## Materials and Method

**Method.** Sweating was stimulated by an intradermal injection of mecholyl hydrochloride, as described in an earlier publication (Anderson and Freeman, 1958); 2 mg. mecholyl was injected intradermally on the forearm in adults and older children and a smaller dose in babies and young children. Sweat was collected for one hour.

Sodium was measured by flame photometry. This estimation can be accurately made in amounts of sweat as small as 50 mg., which was all that could be obtained from some very young infants. In the majority of instances at other ages, over 100 mg. was obtained. Chloride was determined by the method of Schales and Schales. Owing to the relative inaccuracy of titration when chloride levels are low and small amounts of sweat are collected, sodium levels are considered to be the most reliable. Therefore sodium figures only are presented in this paper. There would be no difference in the general pattern of results if chloride figures were also presented but for the sake of clarity and accuracy they are not detailed here.

In our previous publication the level of 70 mEq./l. was chosen as the upper limit of normal and the lower limit of the fibrocystic level, but greater experience has shown that the vast majority of non-fibrocystic children under 15 years give values below 60 mEq./l. sodium, whilst a small percentage of fibrocystic values lie between 60 and 70 mEq./l. Consequently a dividing level at 60 mEq./l. is now taken but all results between 60 and 70 mEq./l. are checked.

**Clinical Material.** The following seven groups were studied:

1. One hundred patients with fibrocystic disease of the pancreas; these were all patients cared for medically

TABLE 1

COMPARISON OF SWEAT SODIUM LEVELS IN CHILDREN WITH FIBROCYSTIC DISEASE OF PANCREAS WITH THOSE OF THEIR SIBLINGS, CONTROL CHILDREN AND CHILDREN WITH CHEST DISORDERS

| Group | No. | Sweat Sodium Levels (mEq./l.) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 0–20 | 20–30 | 30–40 | 40–50 | 50–60 | 60–70 | 70–80 | 80–90 | >90 |
| 'Fibrocystics' .. .. | 100 | 0 | 2 | 0 | 0 | 3 | 7 | 11 | 16 | 61 |
| Controls .. .. | 100 | 28 | 27 | 25 | 11 | 6 | 3 | 0 | 0 | 0 |
| Chronic chest disease | 100 | 23 | 31 | 28 | 15 | 1 | 2 | 0 | 0 | 0 |
| Siblings .. .. | 61 | 8 | 28 | 34 | 12 | 15 | 3 | 0 | 0 | 0 |

Numbers represent % of each group.

by one of us (C.M.A.) during a three-year period. The diagnosis was confirmed by clinical history and examination, and by at least one other test, i.e. the demonstration of pancreatic achylia or deficiency, or of steatorrhoea by laboratory techniques.

2. One hundred children up to 15 years of age used as controls; some of these children showed no organic disease and were tested purely as controls. The others were referred for diagnosis and showed conditions such as coeliac disease, steatorrhoea or failure to thrive. No child with subacute, recurrent or chronic chest symptoms is included in this group. Stools were always examined for excess fat in those who had failed to thrive and all children with steatorrhoea were shown to have normal pancreatic enzymes.

3. One hundred children up to 15 years of age who showed symptoms of subacute, recurrent, or chronic chest disease, but no digestive upsets or clinical evidence of pancreatic deficiency; these children comprise, first, a group, of whom the majority were infants, who were referred for a diagnostic sweat test because they had recurrent attacks of pneumonia or bronchitis; second, a group of patients with proven suppurative bronchiectasis all treated for a number of years by Dr. Howard Williams of the Royal Children's Hospital Chest Clinic; and third, a smaller group of children with chronic asthma who were also patients of the chest clinic.

4. Sixty-one siblings of the patients with fibrocystic disease of the pancreas; these were all under 15 years of age, were healthy, had grown normally and were within normal limits when examined clinically but did not undergo any other test to exclude fibrocystic disease of the pancreas.

5. One hundred adults over 20 years of age with no known disease; these were personnel working in the hospital and relatives and friends of the Clinical Research Unit staff.

6. One hundred parents of the patients with fibrocystic disease of the pancreas; these were all over 20 years of age and did not complain of any persistent diarrhoea or chronic cough.

7. Forty-seven adolescents between 15 and 20 years with no known disease; these were young nurses, office workers, laboratory technicians and school children.

## Results

All groups contained individuals of both sexes in roughly equal numbers, but no difference in sodium or chloride levels was noted between the sexes, although men usually produced a larger volume of sweat than women. Results are given with no further reference to sex.

Among the 100 whose diagnosis was considered to be that of fibrocystic disease of the pancreas and who were all under 15 years of age when first tested, all but five showed levels of sodium and chloride above 60 mEq./litre by the method employed. Sodium results are included in Table 1 where the actual number of children showing various levels are indicated. The two children whose sodium levels are between 20 and 30 mEq./litre were tested twice with similar results. They show other characteristics of the disease, are sisters, have pancreatic achylia and persistent suppurative chest infection of the type so familiar in this disease. The three children with sodium levels between 50 and 60 mEq./litre all have chloride levels above 60 mEq./litre. These children were retested with similar findings in one and higher results in the other two. However, the results recorded are the first performed, as is so with all groups. It can be seen that 95% of sodium values are higher than 60 mEq./litre, 61% being higher than 90 mEq./litre. Table 1 compares these results with the sodium figures obtained from the three other groups of children.

Among the 100 children up to 15 years of age who did not suffer from any chronic chest infection, allergy or pancreatic achylia, 97% of the sweat sodium values are below 60 mEq./litre with 80% below 40 mEq./litre. Among the 100 children with subacute or chronic chest disorders, 98% of sweat sodium values are below 60 mEq./litre with 82% below 40 mEq./litre, a scatter almost identical to that of children without chest symptoms. Among the 61 siblings of the patients with fibrocystic disease 59 or 97% were below 60 mEq./litre, 43 or 70% being below 40 mEq./litre.

Fig. 1 illustrates the results from the three groups of non-fibrocystic children giving a scatter according to age. The overall uniformity of scatter can be seen but as age progresses a somewhat upward trend in

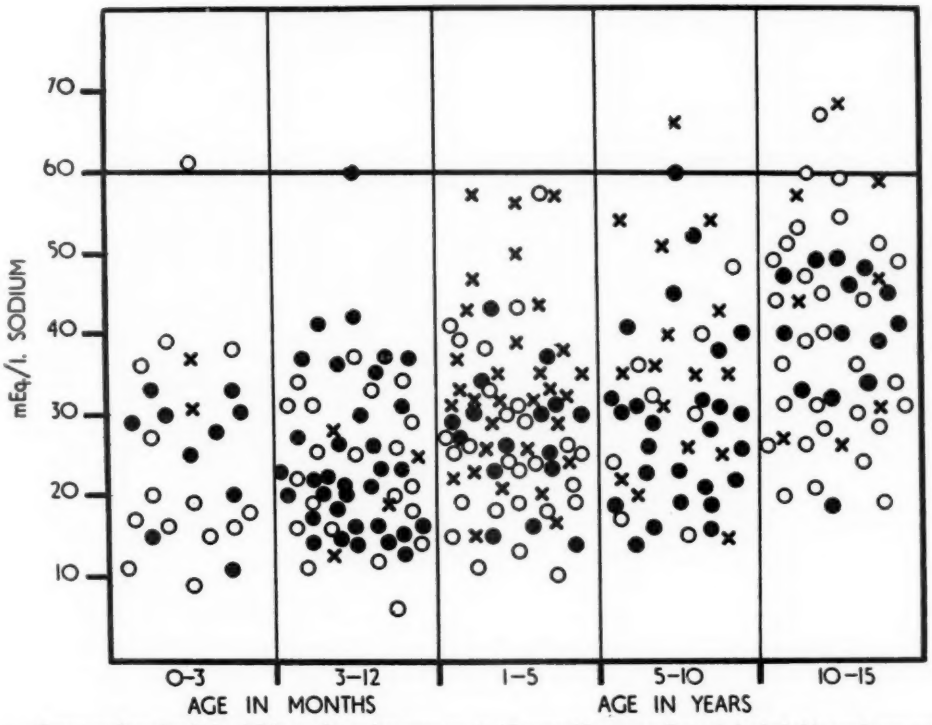


FIG. 1.—Sweat sodium levels in children of varying ages up to 15 years (the upper figure is included in each age group). ○ = normal children; ● = children with chronic chest diseases; x = siblings of children with fibrocystic disease of pancreas.

values occurs in all groups. Combining the three groups it can be seen that up to 12 months of age all but four of the results are below 40 mEq./litre, but after that all age groups show more results between 40 and 60 mEq./litre and in the 10-15 age group about 50% of the values are at that level. Therefore up to the level of puberty the majority of values are below 40 mEq./litre, but there is a tendency for values to increase in later childhood.

There is no difference at all between the scatter of results for children with or without chest illness of non-fibrocystic origin. Among the siblings there are rather more children in the older age groups, for instance, 90% of them are over 12 months compared with 40% of the other two groups combined. Taking this into account there is no significant difference between the results from the siblings and the other groups.

The results from the 100 normal adults (Table 2) and (Fig. 2) show a much wider scatter of results. A considerable number, 34%, were 60 mEq./litre and higher and only 23% were below 40 mEq./litre, a contrast to the non-fibrocystic children. The 100 parents of the fibrocystic children (Table 2 and Fig. 2) show a similar wide scatter of results with 39% over 60 mEq./litre and 19% below 40 mEq./litre. Although a few more results from parents are in the higher levels, notably the 70-80 mEq./litre group, there is a wide scatter of results and above 80 mEq./litre a very similar number to the normal adults. There is therefore no significant difference between the two groups of adults, although they

TABLE 2
COMPARISON OF SWEAT SODIUM LEVELS IN 100 'NORMAL' ADULTS AND 100 PARENTS OF CHILDREN WITH FIBROCYSTIC DISEASE OF THE PANCREAS

| Group | No. | Sweat Sodium Levels (mEq./l.) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 0–20 | 20–30 | 30–40 | 40–50 | 50–60 | 60–70 | 70–80 | 80–90 | >90 |
| 'Normal' adults .. | 100 | 0 | 7 | 16 | 21 | 22 | 12 | 12 | 6 | 4 |
| Parents of children with fibrocystic disease of the pancreas | 100 | 2 | 3 | 14 | 15 | 27 | 14 | 16 | 6 | 3 |

Numbers represent % of each group.

differ significantly from the three groups of children up to 15 years.

The 47 normal adolescents between 15 and 20 years of age show results intermediate between those of the children and the adults with 11 or 24% above 60 mEq./litre and 13 or 27% below 40 mEq./litre (Table 3 and Fig. 2).

Fig. 2 gives the scatter of results of children, adolescents, adults and parents and indicates clearly the gradual increase in levels with age, the greater number of higher results after puberty as well as the wide variation of values in adult life. Table 3 combines all the non-fibrocystic results illustrating again the upward trend of values with increasing age, and shows the percentage of each group giving values below 40 mEq./litre, between 40 and 60 mEq./litre, and above 60 mEq./litre. From these results it can be seen that about puberty and in adult life the level of 60 mEq./litre can no longer

TABLE 3

COMPARISON OF SWEAT SODIUM LEVELS IN ALL GROUPS STUDIED TO SHOW INCREASING VALUES AT AND AFTER PUBERTY

| Group | Sweat Sodium Levels (mEq./l.) | | |
|---|---|---|---|
| | <40 | 40-60 | >60 |
| Control children | 80 | 17 | 3 |
| Children with chronic chest disease | 82 | 16 | 2 |
| Siblings of children with fibrocystic disease of the pancreas | 70 | 27 | 3 |
| 'Normal' adolescents | 27 | 49 | 24 |
| 'Normal' adults | 23 | 43 | 34 |
| Parents of children with fibrocystic disease of the pancreas | 19 | 42 | 39 |

Numbers represent % in each group.

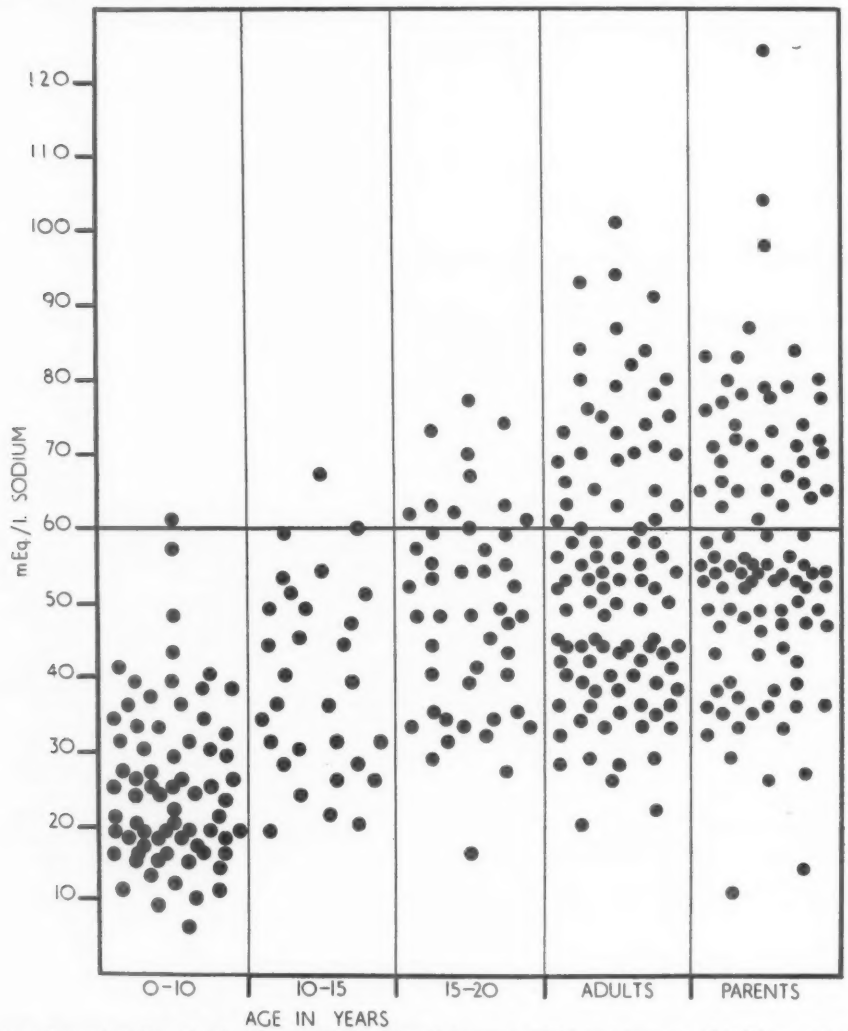


FIG. 2.—Comparison of sweat sodium levels in control children adolescents, adults and parents of children with fibrocystic disease of the pancreas (the upper figure is included in each age group).

TABLE 4

INDIVIDUAL VARIATION IN SWEAT RATE AND COMPOSITION IN FOUR NORMAL ADULTS WITH CONSTANT MECHOLYL STIMULUS

| Date | Temperature and Climate | A | | B | | C | | D | |
|---|---|---|---|---|---|---|---|---|---|
| | | Sweat (g.) | Na Cl (mEq./l.) | Sweat (g.) | Na Cl (mEq./l.) | Sweat (g.) | Na Cl (mEq./l.) | Sweat (g.) | Na Cl (mEq./l.) |
| November 5, 1959 .. .. | 24° C.; slight humidity | 0·1312 | 57 49 | 0·0611 | 56 79 | 0·3862 | 46 32 | 0·3249 | 77 58 |
| November 26, 1959 .. .. | 28° C.; high humidity | 0·1518 | 64 77 | 0·0959 | 67 68 | 0·3724 | 44 47 | 0·6606 | 62 49 |
| December 12, 1959 .. .. | 24° C.; warm and dry | 0·0944 | 45 47 | 0·0414 | 58 53 | 0·3283 | 46 31 | 0·3389 | 90 60 |
| February 2, 1960 .. .. | 24° C.; warm and dry | 0·1110 | 52 35 | 0·0688 | 79 58 | 0·3067 | 36 25 | 0·3395 | 60 41 |

A and B are female. C and D are male.

be considered as the dividing level between a normal and an abnormal level of sweat sodium.

Normal adults included individuals of varying ages up to the seventh decade and parents up to the fifth decade, but an analysis of these into age groups did not reveal any significant difference in levels. The increase in values was gradual in later childhood, becoming greater at puberty, but did not progress further with old age.

Not only were the values from persons over the age of puberty likely to be higher, but results from individuals showed greater variation when repeated at intervals. To illustrate this variation four normal adults were tested at about monthly intervals and the results are recorded in Table 4. Here some indication is given of the climatic conditions of the day and amounts of sweat collected. Both sodium and chloride levels are indicated. This Table shows the considerable lability in sweat levels using as far as possible the same stimulus. No real correlation is seen with the climate, nor the volume of sweat and hence perhaps the rate, as the time of collection was constant.

Levels over 90 mEq./litre among the adults and parents were repeated if possible. There were seven individuals with values in this region. One male parent and one male adult were unavailable for retesting. Three of the other five showed lowered levels of retesting, although still above 60 mEq./litre. The remaining two, one female parent and one adult woman, showed consistent levels. The female parent, the only adult with a sodium level over 120 mEq./litre, was healthy but thin and had never had any chronic chest symptoms nor diarrhoea. A stool was normal in appearance and no fat globules were seen by microscopy. We believe this result to be a normal variant, but it is worthy of further investigation.

Chloride values are not recorded for reasons stated earlier, but the pattern of results in relation to age was very similar. 60 mEq./litre of chloride was still found to be the dividing line between 'fibrocystic' and 'non-fibrocystics' when considering children up to 15 years of age. In adults the sodium and chloride values did not approximate each other quite as closely as they did in children. Among the two groups of adults tested, i.e. 'normals' and 'parents', sodium figures were often slightly higher than chloride figures. However, this did not alter the comparison between the two groups of adults as there was still a comparable number of figures over 60 mEq./litre, for instance, 23% of normal adults and 25% of parents.

## Discussion

Using a constant method of sweat stimulation and collection, levels of sweat sodium have been determined at various ages in childhood, adolescence and adult life. Fairly constant levels in infants and young children are found, but these levels rise slowly as age progresses and become very much more variable after puberty. Although the level of 60 mEq./litre of sodium can be said to be the upper limit of normal in the sweat of children under 15 years, such is not the case in adolescents and adults where many of the values are above this level. In all children under 15 who were tested, whether they are free from disease, suffer from chronic chest disease of non-fibrocystic origin, or are siblings of patients with fibrocystic disease, values are in the same range and 60 mEq./litre can be taken as the upper level. Taking into account the increasing values occurring after puberty there is also no difference in the pattern of results obtained from normal adults and from parents of patients with fibrocystic disease.

The two latter observations are at variance with those reported by some other workers, notably Di Sant'Agnese *et al.* (1953), Di Sant'Agnese (1957, 1959), and Smoller and Hsia (1959) who consider that levels of sodium and chloride in the sweat of some parents and siblings are higher than normal from which they deduce that these individuals are carriers of the abnormal gene of fibrocystic disease; and Hsia *et al.* (1958) who consider that children with chronic or allergic chest disease show higher levels than normal children. Our results, using a much wider range of controls, show no evidence to support these views. It is difficult to reconcile these varying results, but there are some factors which can be discussed.

A possible criticism of our results is that the method of obtaining sweat is not a satisfactory one. Among workers in the field of sweat electrolytes in fibrocystic disease of the pancreas a variety of methods have been used to stimulate sweating, but these fall broadly into two classes: sweating stimulated by heat or by other chemical agents. Results recorded by Di Sant'Agnese and his group and Hsia and co-workers are those of heat sweat. In the present study the method of sweat stimulation by intradermal mecholyl has been chosen for reasons outlined in a previous publication (Anderson and Freeman, 1958). As pointed out in that paper, the levels of sodium and chloride in sweat obtained in this way may be somewhat higher, occasionally up to 20 mEq./litre, than in sweat obtained by heat stimulation. However, this choice of method does not significantly affect the results obtained in the present study because all tests were done in the same way and can therefore be compared with each other, although not necessarily with those of other workers.

It might be possible that heat sweat produces a different pattern of values. However, study of the literature relating to normal sweating reveals a wide divergence in the range of results of sodium and chloride obtained by many workers. Notable amongst these references are the review by Robinson and Robinson (1954) and the monograph on 'Human Perspiration' by Kuno (1956). The former authors state that the concentration of sodium chloride in thermal sweat is extremely variable and give a list of 10 references in which values varying from as high as 100 to 148 mEq./litre down to 5 mEq./litre are reported, all on supposedly normal individuals and mostly adults. Kuno lists three groups of workers who find values as divergent as 400 to 17 mg. % sodium. They both point out the numerous factors such as skin temperature, climatic conditions, dietary intake of salt, and adrenal cortical activity, which can affect these levels and Kuno in particular mentions age, discussing a control mechanism which begins to act on the sweat centres about puberty. Therefore it seems that our results in adults obtained by mecholyl stimulation parallel in the main those of many other workers, who were not concerned with fibrocystic disease of the pancreas.

Precise knowledge of the physiological control of the concentration of electrolytes in sweat has not yet been obtained, but many factors apparently affect these concentrations. The results presented here support Kuno's statement that age may be one of the factors and that about puberty there may be some physiological alteration in the control mechanism, or the factors that influence the concentrations may be playing a greater part, perhaps the endocrine factors. In view of the confusion that exists regarding the precise limits of normal variation of sweat sodium and chloride concentration in adults and the limitations of knowledge regarding the physiological control of these electrolyte levels, it is unwise to draw conclusions from the rather minor differences which some workers have observed in a proportion of parents and siblings of patients with fibrocystic disease and in some patients with chronic chest disease. In the work of both Di Sant'Agnese's group and Hsia and co-workers small groups of control adults are mentioned, but no attention paid to variation over a wide range of age.

A study of the literature devoted to the sweat sodium and chloride levels in patients with fibrocystic disease of the pancreas shows that differing levels are given by several authors as the upper limit of normal. The original contribution of Darling *et al.* (1953) stated that 60-70 mEq./litre of sweat sodium or chloride in heat sweat was the dividing line between normal and abnormal, but in a recent publication from the same centre (Di Sant' Agnese, 1959) the figure of 50 mEq./litre is given without adequate explanation of the change. Similarly, 50 mEq./litre is the upper level stated by Hsia *et al.* (1958) whilst 70 to 80 mEq./litre is the figure given by Shwachman and Leubner (1955). As there is still such variation among workers regarding the upper limit of normal for heat sweat it does not seem reasonable to theorize over levels between 50 and 70 mEq./litre obtained in parents and siblings (Smoller and Hsia, 1959), children with allergic chest conditions (Hsia *et al.*, 1958), or adults with chronic chest disease (Petersen, 1959).

The abnormal gene for fibrocystic disease of the pancreas appears to be a reasonably frequent one in the community and it might be argued that the adults and parents who showed values over 60 mEq./litre

in this paper were all heterozygotes. However, between 30 and 40% of both groups of adults tested came into this category and not even the most enthusiastic geneticist has yet placed the carrier rate at this level. The majority opinion suggests that the incidence of this disease in communities of Caucasian origin is in the region of one in 1,000 live births (Carter, in Bodian, 1953; Childs, 1956) and consequently, as the former writer states, the carrier rate would be about one in 15 or 6·5%.

If these higher results did indicate the carrier state then a proportion of siblings should show results in the same range, but in the data presented here they do not. Apart from the constant and clear difference between fibrocystic and non-fibrocystic children under 15 years of age there does not seem to be any other information relevant to fibrocystic disease of the pancreas than can at present be obtained from a study of the actual levels of sweat sodium and chloride, unless the reason for the varying and high levels found normally after puberty bears any relationship to the underlying defect in this disease.

As a consequence of the data presented here the determination of sweat sodium and chloride loses much of its value as a test for the diagnosis of fibrocystic disease of the pancreas in adults. We have already encountered difficulty in several adolescents and older persons who are suspected by certain clinical features of suffering from this disease. In these a very careful assessment of all features relevant to the disease should be made. As yet, there is insufficient evidence for the postulation of 'formes frustes' of the disease, but this will be discussed in more detail in a future publication.

The sweat abnormality or the abnormality of exocrine secretions in fibrocystic disease of the pancreas cannot yet be explained in basic terms, and until this can be done, slight abnormalities of sweat electrolytes should not be regarded as a genetic manifestation of the disease. Theorizing in this regard has preceded precise basic knowledge, and may give rise to misleading genetic counselling.

## Summary

The range of sweat sodium and chloride levels obtained by stimulation with mecholyl in normal persons from birth to old age has been determined. A slight increase in concentration of these electrolytes has been found with increasing age in childhood. There is a greater increase and variation at and after puberty.

No difference has been observed in the results from 100 normal adults over 20 years of age and 100 parents of fibrocystic children.

No difference has been observed in the results from 61 healthy siblings of fibrocystic children and other children up to 15 years of age.

No difference has been observed in the results from 100 normal children and 100 children with chronic chest illness other than fibrocystic disease of the pancreas.

These results do not provide evidence that the carrier state in fibrocystic disease can be determined from raised levels of sweat sodium and chloride, nor that chest disorders in children show altered levels of these sweat electrolytes.

The 'sweat test' is of limited value in the diagnosis of fibrocystic disease of the pancreas in young adults or older persons.

Generalizations regarding genetic constitution in families of fibrocystic children should await further knowledge of the normal mechanism of control of sweat electrolytes and the basic defect in fibrocystic disease.

We should like to thank Miss R. Thomson for technical help with the electrolyte estimations, and Sister Pollock and her staff for help with the 'sweat tests', the many physicians of the Royal Children's Hospital who have referred patients to us, and the 'normal controls' who volunteered their help.

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# THE SIGNIFICANCE OF INTIMAL THICKENING IN THE ARTERIES OF THE NEWBORN

BY

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From both Europe and North America there have been a number of reports describing the presence of cushion-like areas of intimal thickening and elastic reduplication in the arteries of foetuses and infants (Dock, 1946; Fangman and Hellwig, 1947; Levene, 1956; Robertson, 1960a). The significance of these intimal cushions is uncertain. They are believed by some to be pathological in nature and the early lesions of atherosclerosis. Another view regards them as being a physiological adaptation of the vessel wall to mechanical stress and as having little influence in dictating the later development of atherosclerosis.

At Ibadan, coronary occlusion is rarely seen in the adult African and in the literature there are many reports indicating that atherosclerosis, certainly of the aorta and coronary arteries, is much less severe and extensive in the African Bantu and Negro than in Europeans (Davies, 1948; Edington, 1954; Hannah, 1958; and others). The present investigation sets out to determine whether intimal thickenings occur in the arteries of the African newborn and to compare their incidence with that found in European and North American subjects.

## Methods

The popliteal artery of one leg was examined in 52 newborn African infants, 32 of whom were male and 20 female. Their ages ranged from foetuses of 30 weeks gestation to babies 2 weeks old. Most, however, were full-term stillbirths. In 30 of the cases, 19 male and 11 female, the proximal parts of the anterior descending and circumflex branches of the left coronary artery were also examined. From each vessel a small segment was taken and after fixation in formalin, paraffin sections were prepared and stained by haematoxylin and eosin and Weigert's elastic tissue stain counter-stained by van Gieson.

## Findings

In the newborn the intima of the muscular arteries consists of an elastic membrane, the internal elastic lamina, which is covered by the endothelium. The circular muscle of the media surrounds the intima and is bounded on its outer aspect by the adventitia. Of the 52 popliteal arteries examined, 42 (27 male and 15 female) showed areas in which there was a disturbance of this architecture. The pattern of this varied, but in most instances both the intima and media were affected to form a local cushion-like thickening of the wall. In the intima there occurred a reduplication of the internal elastic lamina so that several coarse lamellae or sometimes numerous fine elastic filaments were formed between which smooth muscle cells could be seen (Fig. 1). In the underlying media bundles of longitudinally orientated muscle also contributed to the thickening

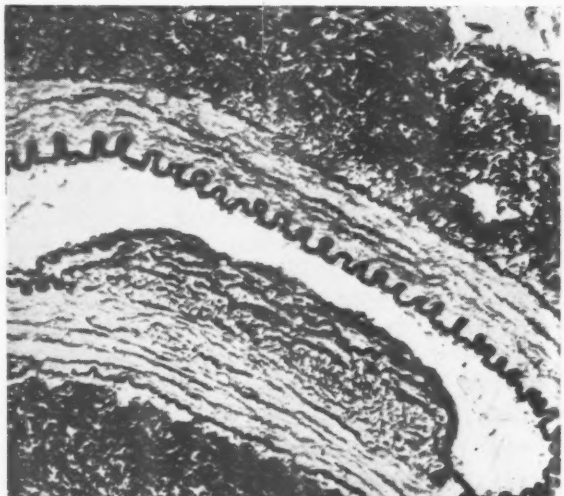

FIG. 1.—Popliteal artery. Full term stillbirth. A cushion-like thickening of the wall is present over which there is reduplication of the internal elastica. (Weigert × 150.)

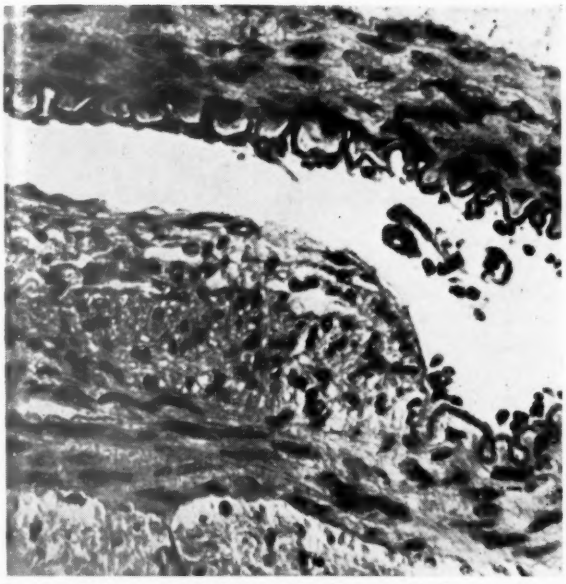

FIG. 2.—High power field of the cushion illustrated in Fig. 1. A band of longitudinal muscle is present in the media beneath the split elastica. (H. and E. × 300.)

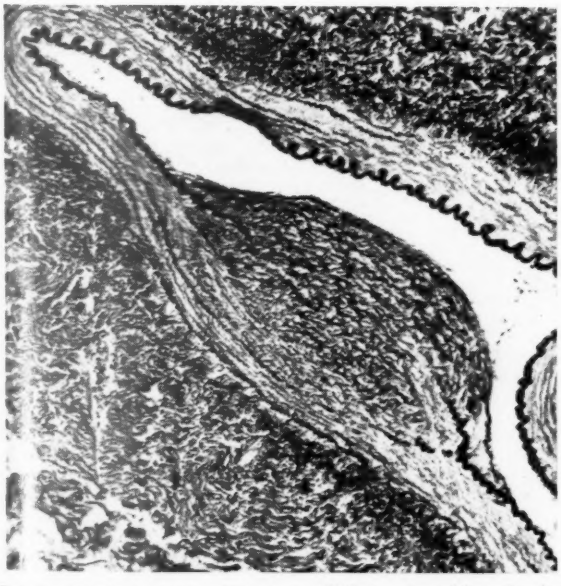

FIG. 3.—Popliteal artery. Full term stillbirth. A cushion showing marked reduplication of the internal elastica. The interstices of the elastic mesh contain many longitudinally orientated muscle cells. (Weigert × 86.)

of the wall (Fig. 2). These longitudinal muscle bundles were the most conspicuous feature of many cushions and in some instances they formed the whole of the thickening, there being no reduplication of the internal elastica. Both the size and complexity of the cushions varied widely, ranging from small nodes of longitudinal muscle in the media to the formation of large musculo-elastic mounds (Fig. 3). They occurred especially at the margins and opposite the mouths of branches, but were apparently not restricted to these sites, although serial sections would have been required to confirm this.

The left coronary artery was examined in 30 subjects and in 16 of these (11 male and five female) cushion-like thickenings of the wall similar to those of the popliteal artery were found. In the coronary vessels reduplication of the internal elastica tended to be more prominent than bundles of longitudinal medial muscle in the formation of the cushions. Only very occasionally, however, did a thickening show no evidence of a medial component. In both the coronary and popliteal vessels the van Gieson stain revealed strands of fibrous tissue in some of the cushions. It was generally associated with the elastic fibrils of the intima. In no instance was it present in large amount and many cushions showed no evidence of a fibrous component.

## Discussion

Two views exist as to the significance of intimal thickenings in the vessels of the newborn. Fangman and Hellwig (1947) and Levene (1956) considered those in the coronary arteries to be pathological and the earliest lesions of atherosclerosis. Dock (1946) and Robertson (1960a) on the other hand, believed that they represented a response of the vessel wall to mechanical stress. In the coronary vessels Dock attributed this stress to the changing length to which these vessels had to adapt themselves during cardiac systole. Robertson, however, described similar thickenings in the popliteal and brachial arteries of the foetus and considered that their function was to buffer a stress due to tugging at the margins of branches and other points of fixation of the vessel during its elongation with pulsation. It was believed that the presence of intimal cushions was of no significance in determining the later development of atherosclerosis, although, if the disease did occur, it tended to localize in these regions of stress (Robertson, 1960b).

In the present study of newborn African subjects, cushion-like thickenings were found in the popliteal and coronary arteries of 81 and 53% of cases respectively. In both vessels the incidence was slightly higher in males than females. From these findings it appears that intimal thickenings occur just as frequently in the newborn of the African Negro as in those of the white races. Thus,

in a series of European foetuses, exactly similar structural changes were found in the popliteal artery of 76% of subjects (Robertson, 1960a) while, in North America, Fangman and Hellwig found coronary thickenings in 12 (40%) of 30 newborn infants, the incidence being higher in males than females. Despite the similar findings in the newborn of both races, most authors are agreed that atherosclerosis is less marked in the African Bantu and Negro than in Europeans. Higginson and Pepler (1954), for example, have found that only 3% of African compared with 32% of Danish subjects of the fourth decade have severe coronary and aortic lesions. The results of the present study therefore support the view that the presence of intimal cushions in the vessels of the newborn plays little part in determining the later development of atherosclerosis.

## Summary

The presence of areas of intimal thickening and elastic reduplication in the popliteal and coronary arteries of newborn African infants is described. Their incidence was found to be similar to that in the newborn of European and North American subjects. The significance of these thickenings in the pathogenesis of atherosclerosis is briefly discussed.

I wish to thank Professor G. M. Edington for his advice and encouragement during the course of this work.

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# HISTIOCYTIC MEDULLARY RETICULOSIS IN A CHILD

BY

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Scott and Robb-Smith (1939), using the name 'histiocytic medullary reticulosis', reported four cases of a subacute illness characterized by fever, anaemia, leucopenia, jaundice and enlargement of the lymph nodes, spleen and liver. Microscopically there was a proliferation of phagocytes and giant cells in the reticulo-endothelial system, the affected tissues showing a tendency to undergo haemorrhage and necrosis. Marshall (1956a, b) described eight cases and referred to seven others reported in the literature since 1939.

The disease has not been reported in children and it is for this reason that the following case is mainly of interest. (For a review of the literature and discussion of various aspects of the disease Marshall's publications, 1956a, 1956b, should be consulted.)

## Case Report

The patient was admitted to the Adelaide Children's Hospital on October 9, 1954, at the age of 4 years 5 months with generalized enlargement of the lymph nodes.

Her previous health had been good, apart from chickenpox and tonsillectomy, until three months before admission when a small lump in the right side of the neck had been noticed by her parents. A month before admission, because of a sudden increase in size of her neck, she was taken to a general practitioner who found rubbery enlargement of five or six lymph nodes in the right side of the neck. He could not feel the spleen at this time. Following treatment with antibiotics the nodes subsided considerably. Two days before admission they enlarged again, accompanied by a fever with a temperature of 102° F., tiredness and loss of appetite.

On admission to hospital the cervical, axillary and inguinal glands were all enlarged and the spleen was felt 3 fingers' breadth below the costal margin. The liver could not be felt. Blood examination showed Hb 10 g./100 ml., the red blood cells numbered 3,800,000 per c.mm. and the white cells 8,800 per c.mm., 61% being neutrophils, 37% lymphocytes and 2% large lymphocytes. No abnormality was seen in a radiograph of the chest. A week after admission the Paul-Bunnell test gave agglutination at a serum dilution of 1 in 32, rising to 1 in 64 three days later. Another blood examination on the day she left hospital, 11 days after her admission, showed Hb 12 g./100 ml., a white cell count of 14,800 per c.mm. of which 45% were neutrophils, 35% lymphocytes, 18% monocytes and 2% abnormal lymphocytes. Apart from two short bursts of fever, up to 100° F., her temperature was normal during her stay. On discharge from hospital her spleen could just be felt at the costal margin and the lymph nodes were much smaller. She was sent home to rest in bed, diagnosed as suffering from infectious mononucleosis.

On November 11, 1954, she returned to hospital with enlargement of the cervical lymph nodes which had apparently occurred over a few hours. Some fever had been noted five days before.

On examination she was pale and had very large fleshy lymph nodes in the right cervical region extending from behind the ear to the supraclavicular fossa. There was also enlargement of the nodes in the right axilla. The left cervical nodes were only slightly enlarged and no enlargement was felt in the inguinal regions. The spleen was enlarged to the level of the umbilicus but the liver could not be felt. The throat and middle ears were not inflamed.

Blood examination soon after admission showed Hb 10 g./100 ml. and a white cell count of 8,200 per c.mm.; bone marrow smears were normal. Further blood examinations during her illness showed a progressive fall in red and white cells and a later fall in platelets; Fig. 1 shows some of these changes. Reticulocytes never made up more than 2% except on one occasion when they reached 4% of the total red cell count. Four days after admission the lymph nodes were smaller but one from the right side of the neck was removed. Microscopical examination revealed that the general architecture of the node had been destroyed apart from some remaining cortical lymphoid follicles. In one part of the cortex was a wedge-shaped area of fibrosis containing scattered plasma cells. Elsewhere there was a mixed population of lymphocytes and plasma cells in an inconspicuous mesh of reticular cells, amongst which were scattered large, sometimes binucleated, mirror-imaged 'reticulum' cells. Reticulin fibrils were increased.

Fever began on November 22, the temperature remaining between 100° and 104° F., with rare falls to normal, until her death. No infective cause for this was found.

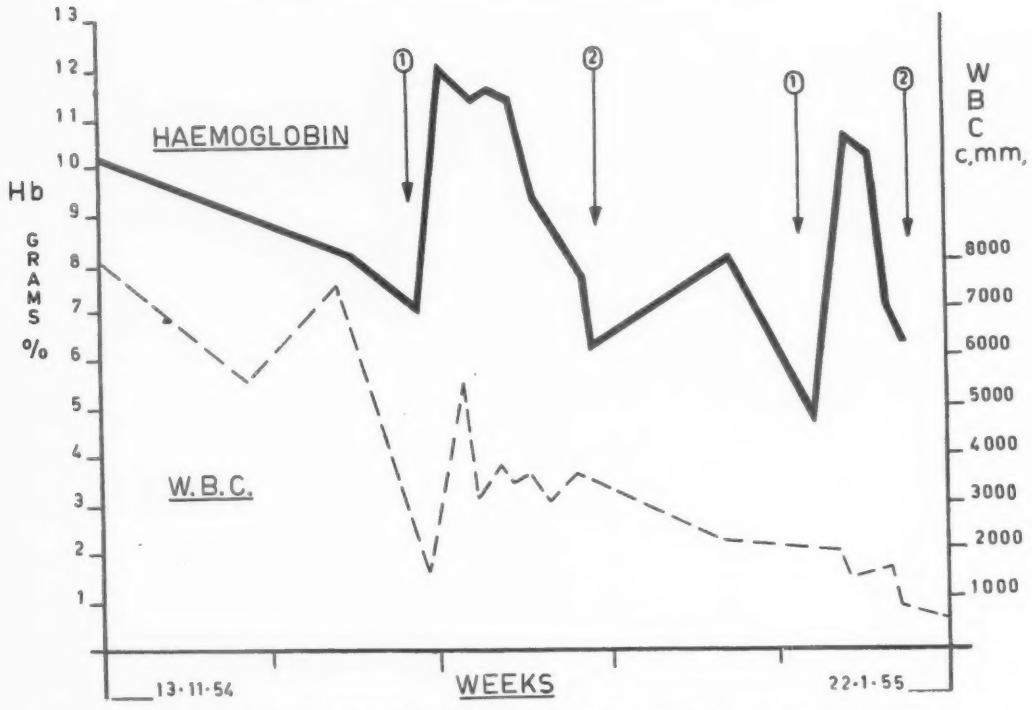


FIG. 1.—Haemoglobin and white count during final hospitalization. The numbered arrows indicate pints of transfused blood.

Blood cultures were negative and her serum did not agglutinate suspensions of *Salmonella* or *Brucella* organisms. In spite of the fever the lymph nodes and spleen began to subside on December 2, the spleen being just palpable by December 9, and the lymph nodes very small. A further aspirate of bone marrow on December 13, contained 27% monocyte-like forms, 13% lymphocytes, 41% polymorphonuclear white cells (with no excess of blast forms), 18% normoblasts and 1% plasma cells. Many of the monocytic forms had ingested red blood corpuscles, normoblasts, neutrophils and platelets (Fig. 2). A platelet count at this time was 120,000 per c.mm. A mild jaundice was noticed on December 22, and this increased steadily. By January 10, 1955, she was extremely wasted and deeply jaundiced; the lymph nodes had again enlarged to the size of marbles and the spleen and liver were easily felt. On January 13, a month since the last platelet count, the number had fallen to 14,000 per c.mm. and did not rise above this level again. At this time purpura and bruising appeared, followed by epistaxes and bleeding from injection sites. A direct Coombs test and a test of red cell fragility, both giving negative results, were not done until a few days before death, which occurred on January 21, 1955.

**Findings at Necropsy.** The autopsy (A.C.H. No. 8/55) was performed 60 hours after death. The body was extremely emaciated, deeply jaundiced, with numerous petechial haemorrhages in the skin. The pleural and abdominal cavities contained clear orange effusions. The enlargement of the lymph nodes involved all groups, the cervical and axillary glands being most affected and the lower abdominal and inguinal nodes least. The cut surfaces of the glands were firm, pink to brownish purple with ill-defined yellow areas of necrosis. A few nodes were uniformly yellowish. The greatly enlarged spleen weighed 260 g., the serosal and cut surfaces showing irregular shaped yellowish areas up to 0·5 cm. in diameter, scattered over a dark purple background. The liver was enlarged and pale fawn, weighing 670 g. The sternal marrow was pale. The lateral muscles of the right thigh were soft and greyish, the overlying subcutaneous tissue haemorrhagic and the skin vesiculated, these changes being considered due to haemorrhage and infection at the site of injections. Both middle ears, but particularly the right, contained greenish pus from which a *Proteus* organism was isolated. Other organs showed no abnormalities apart from the effects of jaundice and anaemia.

Microscopically, identical changes were found in the lymph nodes and spleen. The architecture of the organs was largely replaced by a loose-textured moderately cellular tissue in which there was much haemorrhage and coagulation necrosis. The necrotic areas, particularly in the spleen, resembled small infarcts. The cellular areas consisted of a loose apparently syncytial proliferation of reticular cells, having oval vesicular nuclei and eosinophilic cytoplasm. Amongst this were typical macrophages which varied in number from place to place and many of which contained red cells and nuclear debris (Fig. 3). Another conspicuous but less numerous element was a giant cell having a large and

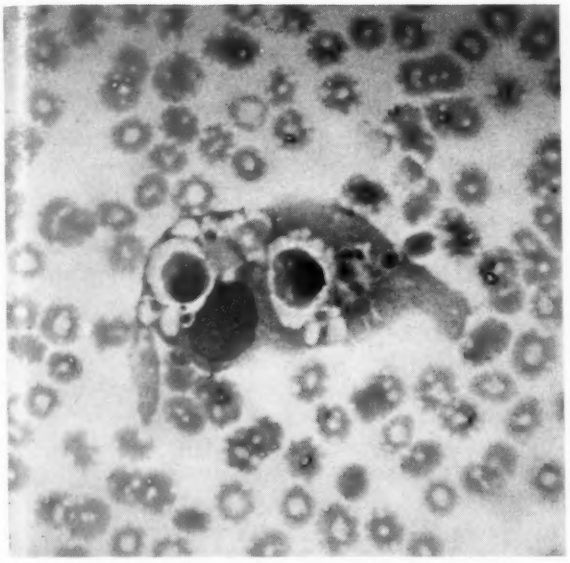

FIG. 2.—Bone marrow smear, showing a large phagocyte containing two red blood corpuscles, two normoblasts and platelets. (Giemsa ×750.)

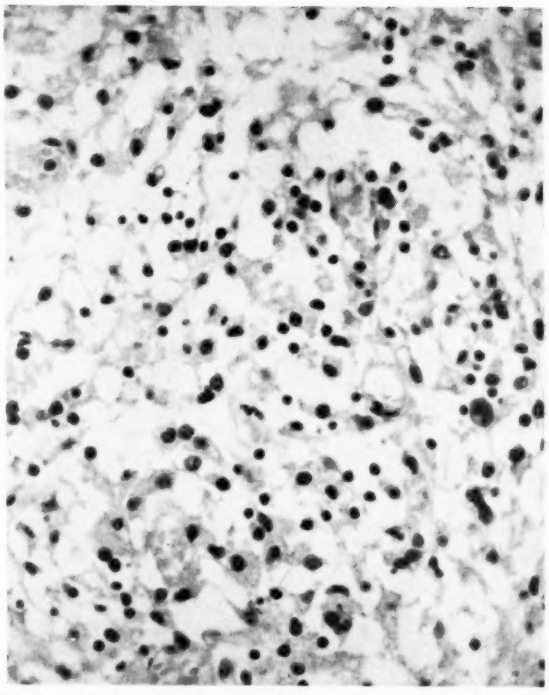

FIG. 3.—Lymph node, showing reticular arrangement of histiocytes. (H. and E. ×330.)

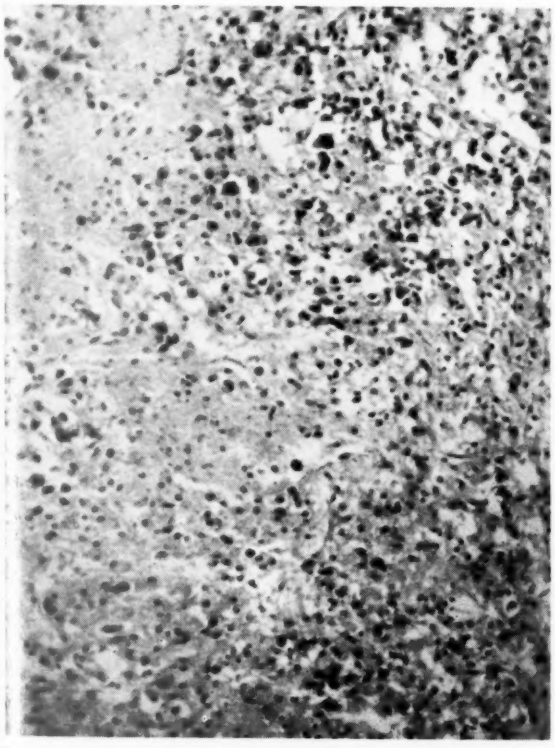

FIG. 4.—Lymph node, showing necrotic areas and densely staining giant cells. (H. and E. ×150.)

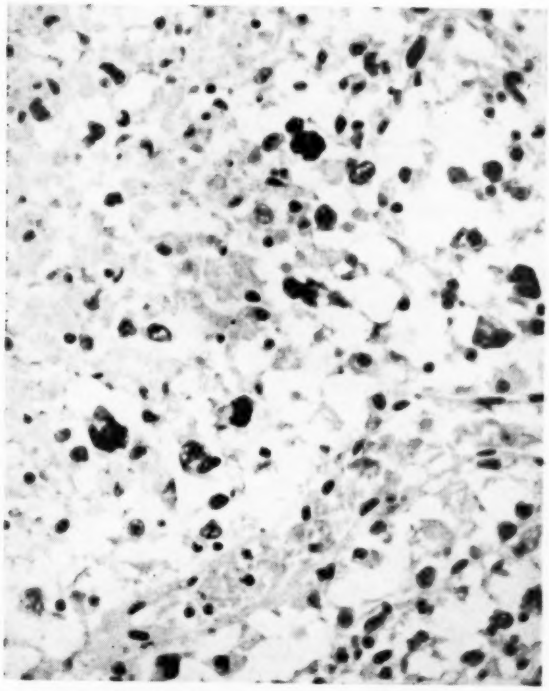

FIG. 5.—Lymph node, showing the irregular-shaped hyperchromatic nuclei of the giant cells. (H. and E. ×330.)

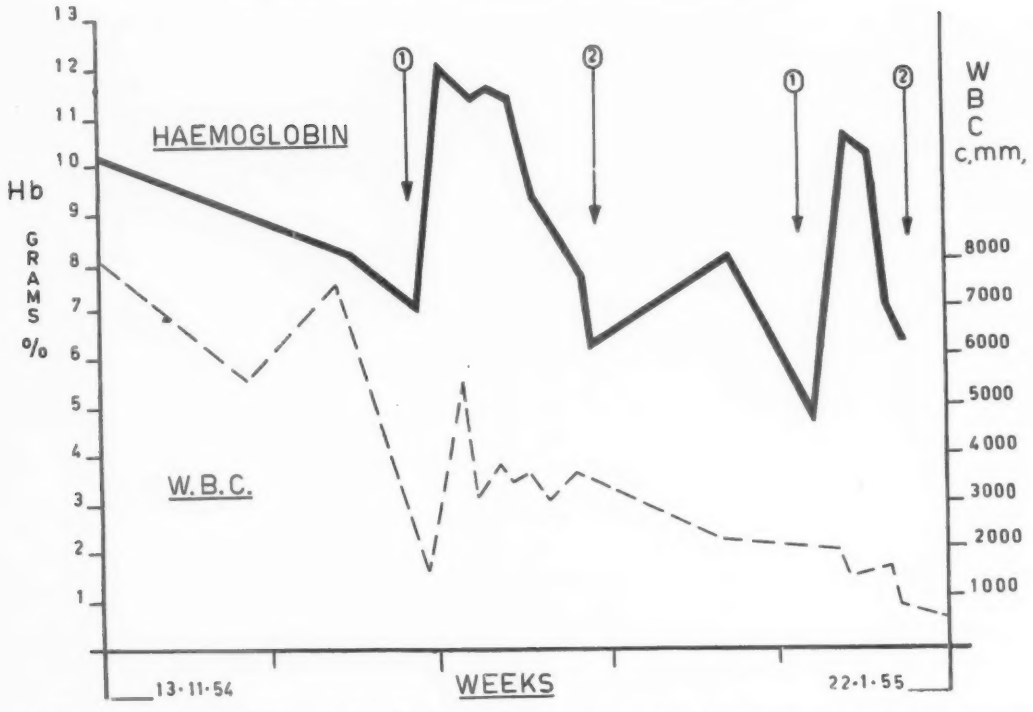


FIG. 1.—Haemoglobin and white count during final hospitalization. The numbered arrows indicate pints of transfused blood.

Blood cultures were negative and her serum did not agglutinate suspensions of *Salmonella* or *Brucella* organisms. In spite of the fever the lymph nodes and spleen began to subside on December 2, the spleen being just palpable by December 9, and the lymph nodes very small. A further aspirate of bone marrow on December 13, contained 27% monocyte-like forms, 13% lymphocytes, 41% polymorphonuclear white cells (with no excess of blast forms), 18% normoblasts and 1% plasma cells. Many of the monocytic forms had ingested red blood corpuscles, normoblasts, neutrophils and platelets (Fig. 2). A platelet count at this time was 120,000 per c.mm. A mild jaundice was noticed on December 22, and this increased steadily. By January 10, 1955, she was extremely wasted and deeply jaundiced; the lymph nodes had again enlarged to the size of marbles and the spleen and liver were easily felt. On January 13, a month since the last platelet count, the number had fallen to 14,000 per c.mm. and did not rise above this level again. At this time purpura and bruising appeared, followed by epistaxes and bleeding from injection sites. A direct Coombs test and a test of red cell fragility, both giving negative results, were not done until a few days before death, which occurred on January 21, 1955.

**Findings at Necropsy.** The autopsy (A.C.H. No. 8/55) was performed 60 hours after death. The body was extremely emaciated, deeply jaundiced, with numerous petechial haemorrhages in the skin. The pleural and abdominal cavities contained clear orange effusions. The enlargement of the lymph nodes involved all groups, the cervical and axillary glands being most affected and the lower abdominal and inguinal nodes least. The cut surfaces of the glands were firm, pink to brownish purple with ill-defined yellow areas of necrosis. A few nodes were uniformly yellowish. The greatly enlarged spleen weighed 260 g., the serosal and cut surfaces showing irregular shaped yellowish areas up to 0·5 cm. in diameter, scattered over a dark purple background. The liver was enlarged and pale fawn, weighing 670 g. The sternal marrow was pale. The lateral muscles of the right thigh were soft and greyish, the overlying subcutaneous tissue haemorrhagic and the skin vesiculated, these changes being considered due to haemorrhage and infection at the site of injections. Both middle ears, but particularly the right, contained greenish pus from which a *Proteus* organism was isolated. Other organs showed no abnormalities apart from the effects of jaundice and anaemia.

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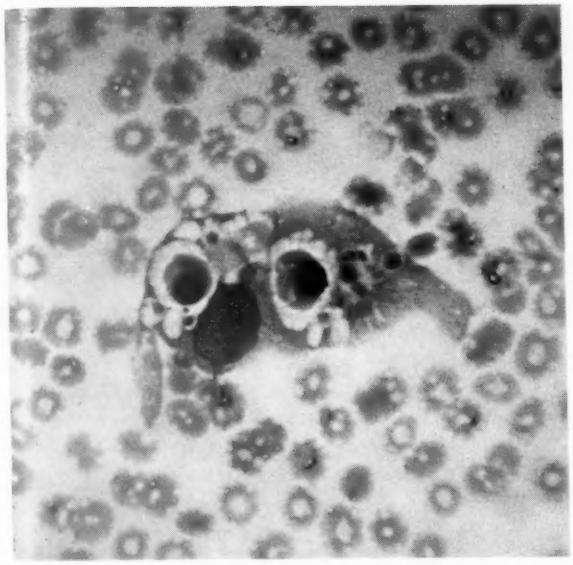

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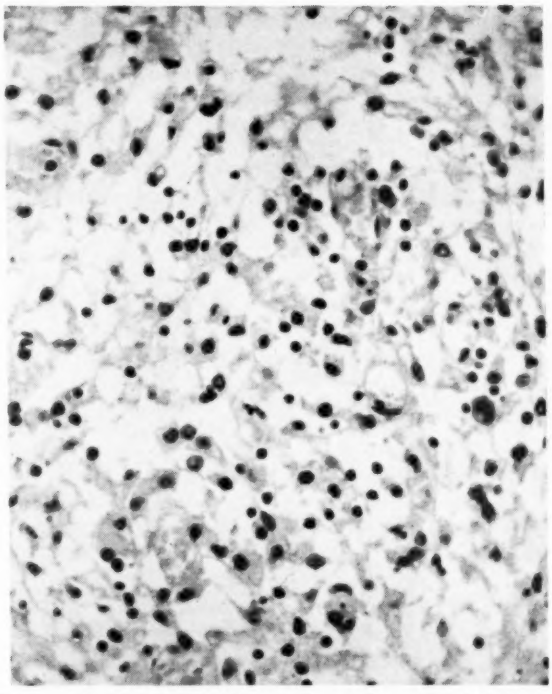

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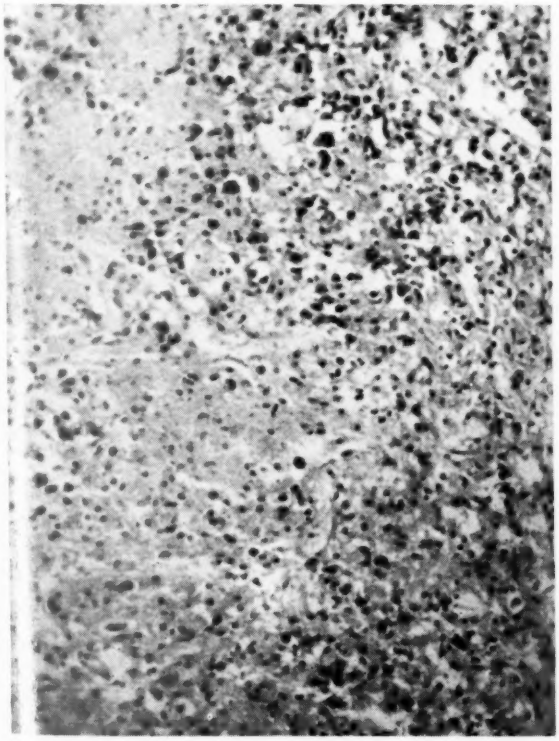

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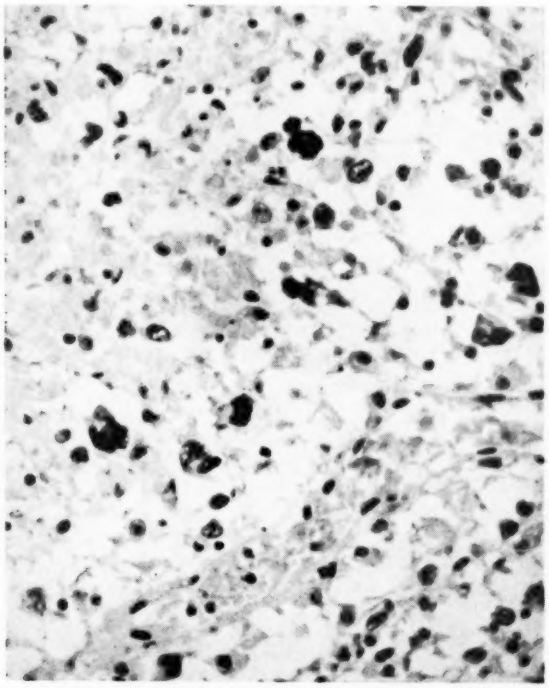

FIG. 5.—Lymph node, showing the irregular-shaped hyperchromatic nuclei of the giant cells. (H. and E. ×330.)

hyperchromatic nucleus and a small amount of eosinophilic or occasionally basophilic cytoplasm (Fig. 4). The nucleus of the cell was commonly irregularly notched or folded, and if, as sometimes occurred, several nuclei were present these were closely packed together and unequal in size (Fig. 5). Transitions between these three main types of cell could be seen. Phagocytosis by the giant cells was not observed. Moderate numbers of mitotic figures were found, mostly in large cells. Mixed with this meshwork of histiocytic cells were small numbers of lymphocytes and many plasma cells and plasmablasts. A notable feature of the abnormal tissue was the large number of thin-walled blood vessels. In the lymph nodes the peripheral sinuses were usually preserved and contained many macrophages. In the spleen a few lymphoid follicles remained.

The sternal marrow showed almost complete replacement by tissue similar to that in the spleen and lymph nodes, except that giant cells were rare.

The liver had undergone a moderate degree of fatty change and congestion, and in addition contained occasional small haemorrhagic and necrotic foci of histiocytes and giant cells. Similar groups of tumour cells were found in the suprarenal cortex. Phagocytosis of red cells by Kupffer cells was present throughout the liver.

Other organs contained no significant changes. Perl's stain for iron revealed much haemosiderin in the spleen and Kupffer cells, but very little in the lymph nodes. Reticulin fibrils were increased in the lymph nodes.

## Discussion

The clinical and pathological findings in this case conform in every way to the previous descriptions of the disease, except for the age of the patient. It is not proposed here to discuss the relation of this condition to other reticuloses; the pathological findings in the reticulo-endothelial organs are, however, quite singular. Nevertheless, the histological changes in the cervical lymph gland of the present case were considered by several pathologists to be typical of classical Hodgkin's disease, appearances which were to be completely replaced by the time of death two months later.

The relapsing nature of the illness also calls for attention, indicating that the course of the disease cannot be fully explained by neoplastic proliferation. The sudden enlargement of the spleen and lymph nodes may have been partly due to vascular engorgement rather than cellular proliferation alone. The equally sudden return of these organs to relatively normal size is hard to explain on other grounds.

The preliminary diagnosis of infectious mononucleosis could not be maintained, particularly as the Paul-Bunnell tests were performed with non-absorbed sera.

The rapid fall of the haemoglobin level following transfusions (see Fig. 1) suggested that the anaemia was due not solely to replacement of the bone marrow and this was confirmed pathologically by the discovery of widespread erythrophagocytosis and haemorrhage.

## Summary

A girl of 4½ years presented with enlargement of the cervical lymph nodes and spleen, followed by anaemia, leucopenia, fever and enlargement of the liver. Jaundice, thrombocytopenia and a bleeding tendency appeared terminally.

A lymph node removed during life showed appearances typical of Hodgkin's disease but at death the reticulo-endothelial system was replaced by a proliferation of phagocytic histiocytes and giant cells.

I am grateful to Dr. Malcolm Cockburn for the use of the case record and to the Board of the Adelaide Children's Hospital for permission to publish the material. Thanks are due to Mr. Ray Boyd for the preparation of the illustrations.

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# DEFICIENCY OF VITAMIN $B_{12}$ AFTER EXTENSIVE RESECTION OF THE DISTAL SMALL INTESTINE IN AN INFANT

BY

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Man may survive resection of surprisingly large amounts of the small intestine. As little as 7 in. of jejunum and ileum may be sufficient to support life, at least for a time (Jackson, Linder and Berman, 1951), and a large number of patients have survived less extensive resections and have remained well (Flint, 1912; Haymond, 1935; West, Montague and Judy, 1938; Althausen, Uyeyama and Simpson, 1949). These observations have been made in adults and the results of extensive resections in children during the growing period are less certain. Such operations are infrequently carried out and there is a high immediate postoperative mortality (Benson and Sharpe, 1950). Children may, however, survive resection of large amounts of the small intestine (Blayney, 1901; Flint, 1912), and two infants have recently been recorded whose growth and development were normal after resection of all but 26 to 28 cm. of jejunum and ileum (Pilling and Cresson, 1957).

The purpose of this paper is to describe a child who had an extensive resection of the distal small intestine soon after birth. She later developed a mild megaloblastic anaemia associated with severe $B_{12}$ deficiency and required treatment with vitamin $B_{12}$. Her growth and development have been otherwise normal up to the age of $2\frac{1}{2}$ years.

## Materials and Methods

Haematological methods were those described by Dacie (1956); serum vitamin $B_{12}$ levels were measured by microbiological assay using the *Z* strain of *Euglena gracilis*, according to the method described by Hutner, Bach and Ross (1956); glucose tolerance tests were carried out as described by King and Wootton (1956).

Fat balances were carried out over a continuous nine-day period. The child was given a diet containing approximately 30 g. of fat daily. After a preliminary period of three days, the stools were collected over successive three-day periods and the fat content was estimated by the method of Van de Kamer, Huinink and Weyers (1949).

Absorption of radioactive vitamin $B_{12}$ was measured by the modified faecal excretion technique described by Booth and Mollin (1956). The test dose of vitamin $B_{12}$ was 1 μg. and was given with 50 mg. of a potent intrinsic factor concentrate.

## Case Report

V.R., a female infant, was born at term on March 31, 1957, after a normal pregnancy (birth weight 7 lb. 5 oz.). Soon afterwards she developed signs of intestinal obstruction and was admitted to West Herts Hospital under the care of Dr. M. E. Edmunds. Laparotomy was performed on the 20th day of life and revealed congenital malrotation of the gut with volvulus and extensive gangrene of the small intestine. Approximately four-fifths of the distal small intestine were thought to have been removed, end-to-side anastomosis being performed between the jejunal stump and the mid-transverse colon. The terminal ileum was closed just proximal to the ileocaecal valve. After an initial period of severe vomiting and diarrhoea, she recovered from the operation, breast feeding was established and she gained weight.

At the age of 3 months she attended The Hospital for Sick Children, Great Ormond Street. At this time she was passing two to five bulky fluid stools daily. She weighed 9 lb. 4 oz., and apart from some abdominal distension, no abnormality was found on examination. She continued with breast feeding and supplements of vitamins A, C and D by mouth. By the age of 6 months her weight (15 lb.) was above the 10th percentile level. Although she continued to have diarrhoea, her weight increased at a normal rate until she was 10 months old, when she weighed 19 lb. (Fig. 1). During the 11th month, however, there was a gradual diminution in the frequency of her stools; she began to vomit after her feeds and she lost weight. She was then admitted to The Hospital for Sick Children at the age of 11 months under the care of Dr. P. R. Evans.

**Clinical Examination.** This revealed a thin child (weight 16 lb. 10 oz.) with generalized abdominal

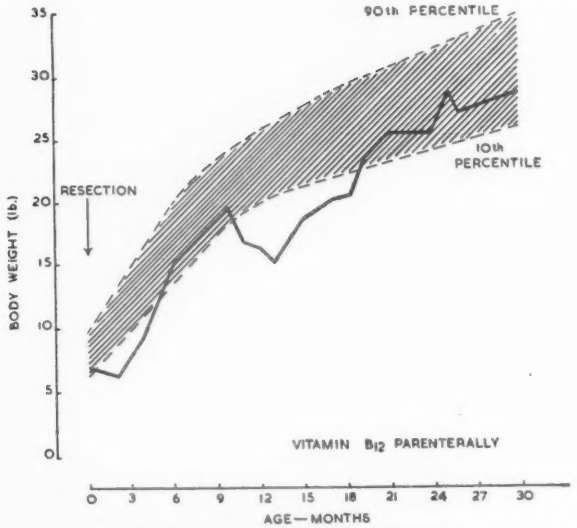


FIG. 1.—Weight chart of patient V.R. after extensive resection of the distal small intestine. Vitamin $B_{12}$ was given parenterally after the thirteenth month. The lines representing the 10th and 90th percentile are also shown (Tanner, 1958).

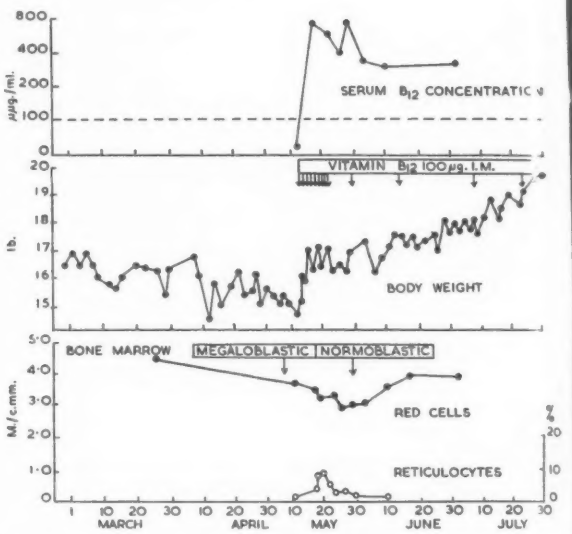


FIG. 2.—Serum $B_{12}$ concentration, body weight, red cells and reticulocytes before and after treatment with vitamin $B_{12}$.

distension. No peristalsis was visible. There was no glossitis nor angular stomatitis. The skin was normal and the central nervous system showed no abnormalities.

**Investigations.** These revealed Hb 12·1 g. % and R.B.C. 4·0 M. per c.mm.; serum electrolytes: Na 140, K 4·2, Cl 102 and $HCO_3$ 26 mEq./litre. Stool cultures were repeatedly negative for pathogenic organisms. Plain radiographs of abdomen showed gross gaseous distension with fluid levels in both colon and small intestine.

**Treatment and Progress.** She was first given oral neomycin (20 mg./lb. body weight in divided doses), but without improvement in her condition. The vomiting, periods of constipation and the radiological evidence of fluid levels in the bowel suggested a diagnosis of subacute intestinal obstruction. A further laparotomy was therefore performed on March 19, 1958, but although the whole of the large bowel and the jejunum immediately proximal to the anastomosis appeared dilated, no organic obstruction was found. The remaining small intestine consisted of the duodenum and approximately 30 in. of jejunum, the end of the jejunum being anastomosed to the middle of the transverse colon, thereby short circuiting the caecum, ascending colon and proximal half of the transverse colon. Nothing further was done and the abdomen was closed.

Her condition continued to deteriorate after this operation. Her weight fell steadily (Fig. 1), vomiting continued intermittently and her stools were bulky and irregular. However, barium meal showed the small intestine to be normal, the barium passing into the colon in one and a half hours. A barium enema outlined the dilated colon but some of the barium remained for five days in the short-circuited ascending colon and caecum, indicating stasis in this loop.

By May 1958, at the age of 13 months, her weight had fallen to 15 lb. (Figs. 1 and 2). Haematological investigations now revealed a mild macrocytic anaemia (Hb 11·0 g. %; R.B.C. 3·7 M. per c.mm.) and the bone marrow was megaloblastic. Her serum $B_{12}$ concentration was 25 µµg. per ml. (normal range 140 to 900 µµg. per ml.). Intestinal function tests were carried out at this time and are shown in Fig. 3. Her absorption of glucose was normal but she had steatorrhoea (mean fat absorption 82% on diet of 30 g. per day) and she was unable to absorb any of the test dose of vitamin $B_{12}$ (Fig. 3).

**Response to Vitamin $B_{12}$.** She was treated with intramuscular injections of vitamin $B_{12}$ (100 µg. daily for nine days, then 100 µg. every two weeks). Her initial response to this treatment is shown in Fig. 2. Vomiting ceased within 24 hours of the first injection and her weight began to increase. Her reticulocytes rose to 9% on the sixth day and the marrow became normoblastic. Although her red cell count fell at first, possibly as a result of rehydration, it then rose to normal levels without other treatment (Fig. 2).

Further investigations revealed no evidence of other deficiencies. Her total serum proteins were 7·0 g. %, serum Ca 8·8 mg. %, inorganic phosphate 5·6 mg. %, and alkaline phosphatase 24 King-Armstrong units. Skeletal radiographs revealed no evidence of rickets. Prothrombin time was normal. Intestinal function studies were repeated after oral chlortetracycline (20 mg./lb. in divided doses for six days). There was no improvement in absorption of either fat or $B_{12}$ following this treatment (Fig. 3).

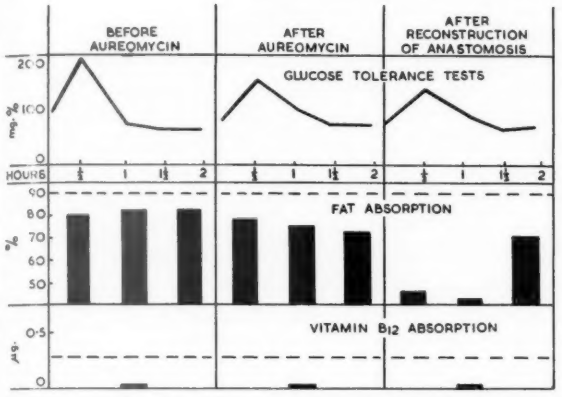


FIG. 3.—Intestinal function tests before and after chlortetracycline (aureomycin) and after refashioning of the jejuno-colic anastomosis. The figures for fat absorption represent the mean absorption per day over successive three-day periods. Normal fat absorption should be greater than 90%. The lower limit of the absorption of radioactive $B_{12}$ by control subjects is indicated by the interrupted line.

Her weight increased steadily, although her stools were unchanged, and she weighed 19 lb. after two months' treatment with vitamin $B_{12}$ (Fig. 2). A further laparotomy was performed on July 30, 1958 (Mr. G. H. Macnab). The jejuno-transverse anastomosis was undone, and an end-to-end anastomosis was made to the caecum. During this procedure many adhesions around the jejunum were broken down. The jejunum appeared slightly hypertrophied immediately proximal to the anastomosis, but the remaining small bowel was of normal calibre. A biopsy taken from the lower end of the jejunum showed normal mucosa, but some hypertrophy of the muscle coats.

She recovered well from this procedure and continued to improve, although a fat balance revealed more marked steatorrhoea than before the operation (mean fat absorption 52% on diet of 30 g. per day). Her glucose absorption remained normal, but she was still unable to absorb vitamin $B_{12}$ (Fig. 3).

After this operation she received a diet usual for her age with restriction of fat to 30 g. per day, together with oral supplements of vitamins A (7,000 units daily), B (Becosym 1 dram daily) and D (1,000 units daily). She was also given vitamin $B_{12}$ intramuscularly (100 µg. every two weeks). Her subsequent progress is shown in Fig. 1. By 20 months her weight was above the 10th percentile and her development has continued normally. Now at the age of 2½ years, she weighs 28·5 lb., a normal weight for her age. Her Hb is 10·9 g. % and she remains well, although she still passes three bulky stools daily.

## Discussion

Estimations of the amount of small intestine remaining after resection are notoriously inaccurate (Flint, 1912). At our patient's first operation, it was considered that four-fifths of the small intestine had been removed. The remaining intestine was measured at a later laparotomy and was found to consist of approximately 30 in. of jejunum. The exact length of the small intestine in an infant is not certain and the proportion of the bowel remaining in this patient is therefore not known, but in this case 30 in. may possibly represent between a quarter and a third of the total small intestine.

The type of malabsorption from which she suffered was characteristic of an extensive resection of the distal small intestine (Booth, 1958). Since some of her proximal intestine remained, she absorbed glucose normally, for glucose is rapidly absorbed from the upper small intestine (Verzár and MacDougall, 1936). Her remaining intestine was apparently only sufficient to absorb between 52 and 82% of her dietary fat and she therefore had steatorrhoea, suggesting that fat is normally absorbed more distally than glucose in the small intestine. Her inability to absorb vitamin $B_{12}$ is in keeping with the resection of the distal small intestine, for $B_{12}$ is absorbed in the ileum in man (Booth and Mollin, 1959).

Stagnant loops of bowel may sometimes play a part in causing malabsorption (Cameron, Watson and Witts, 1949; McIntyre, Sachs, Krevans and Conley, 1956; Halsted, Lewis and Gasster, 1956), but do not appear to have been a factor in this case. In patients with such loops, malabsorption is frequently improved by a course of oral broad spectrum antibiotics (Mollin and Baker, 1955; McIntyre *et al.*, 1956; Halsted *et al.*, 1956; Booth and Mollin, 1957) or by operations which remove or correct the loop (McIntyre *et al.*, 1956). Our patient's absorption defects were not improved by antibiotics, nor by the removal of the short circuit at her last operation, and it seems unlikely that the short-circuited area of colon contributed to her malabsorption. The reason for her deterioration in fat absorption after this operation is uncertain, but it may be that the breaking down of adhesions around the lower jejunum resulted in more rapid passage of food through the remaining small intestine.

For the first 10 months of life her growth was normal, suggesting that she was able to absorb or derive from tissue stores sufficient nutrients to maintain normal development during this time. Since she was unable to absorb vitamin $B_{12}$, it is not surprising that she ultimately developed $B_{12}$ deficiency. The delay in onset of this deficiency was presumably due to the time required to exhaust the stores of vitamin $B_{12}$ in liver and other tissues, a situation which is analogous to the delayed development of $B_{12}$ deficiency after total gastrectomy (Pitney and Beard, 1955). The symptoms and

signs in our patient were different from those usually found in adult patients with Addisonian pernicious anaemia. She had vomiting, constipation and signs suggestive of intestinal obstruction, and she lost weight steadily. There were no neurological signs suggesting subacute combined degeneration of the cord or peripheral neuritis. Despite her very low serum $B_{12}$ level, she was not markedly anaemic, her red cells never falling below 3·0 M. per c.mm., although her sternal marrow was megaloblastic.

Her full and complete response to parenteral injections of vitamin $B_{12}$ suggests that although she had marked steatorrhoea, the only deficiency state she had developed was $B_{12}$ deficiency. This observation is supported by the absence of hypoproteinaemia, her normal prothrombin time and the lack of evidence of rickets. Since she has continued to grow normally whilst receiving only vitamin $B_{12}$ parenterally, she appears to be absorbing the other nutrient factors required for growth and development. These factors, including the vitamins other than $B_{12}$, must therefore be absorbed in the proximal small intestine or colon.

It is not certain whether there is any compensatory improvement in intestinal function in children after extensive resections, although adults may show a progressive increase in absorptive capacity following such operations (Althausen, Doig, Uyeyama and Weiden, 1950). It is said that the mucosa and muscle of the remaining gut typically hypertrophies (Flint, 1912; Jackson, 1958), but this does not always occur (Shonyo and Jackson, 1950; Shelton and Blaine, 1954) and in animals the site of the resection may play a part in determining whether there is hypertrophy of the remaining small bowel (Booth, Evans, Menzies and Street, 1959). In our patient, the barium follow-through showed no evidence of hypertrophy of the small intestine, but at laparotomy the lower jejunum was found to be hypertrophied. It is uncertain whether this was due to partial obstruction by the many adhesions found in this area at her last operation, or whether there has been hypertrophy which was compensatory to the loss of intestinal length. It seems unlikely that she will recover the ability to absorb vitamin $B_{12}$ and treatment with vitamin $B_{12}$ by injection is to be continued indefinitely.

The observations in this patient illustrate the importance of the distal intestine in the absorption of vitamin $B_{12}$. They also support the conclusion that patients who have undergone resection of the ileum should either be kept under close haematological supervision or be treated with prophylactic injections of vitamin $B_{12}$.

**Summary**

Extensive resection of the distal small intestine was performed in a child soon after birth. Her growth was normal until she was 10 months old when she began to vomit and lose weight. At the age of 13 months she was found to have a mild megaloblastic anaemia and her serum $B_{12}$ concentration was very low. She improved dramatically after treatment with parenteral $B_{12}$ and her growth and development have been normal to the age of $2\frac{1}{2}$ years.

We wish to thank Dr. P. R. Evans and Mr. G. H. Macnab for permission to record details of this patient who was under their care in The Hospital for Sick Children, Great Ormond Street; we are also indebted to Dr. D. L. Mollin for his encouragement and advice, and for permission to quote the results of vitamin $B_{12}$ studies carried out in his laboratory at the Postgraduate Medical School.

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# CHRONIC NON-HAEMOLYTIC JAUNDICE WITH CONJUGATED BILIRUBIN IN THE SERUM AND NORMAL LIVER HISTOLOGY: A CASE STUDY

BY

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Recently our knowledge of bilirubin metabolism has increased considerably. Perhaps the most stimulating discovery has been that bilirubin is excreted in the bile as a glucuronide (Billing, Cole and Lathe, 1957; Schmid, 1957). This has made it possible to classify some rare types of chronic jaundice more definitely. One of these, chronic non-haemolytic familial jaundice, was described many years ago by Gilbert and Lereboullet (1901). Arias and London (1957) concluded from *in vitro* experiments with liver tissue that the cause of this disease was a defect in glucuronide formation. The inability to form glucuronides is also present in the much more severe type of inherited chronic jaundice with kernikterus described by Crigler and Najjar (1952) (cf. Axelrod, Schmid and Hammaker, 1957).

Neonatal jaundice also belongs to this group, characterized by insufficiency of glucuronyl-transferase in the liver (Dutton, 1959), but, in contrast to the diseases mentioned above, is a passing phenomenon, present only in the newborn period (Vest, 1958; Vest and Streiff, 1959).

There is another group of chronic non-obstructive, non-haemolytic jaundice in which no such defect in glucuronide formation is present. In consequence a substantial percentage of 'direct' reacting bile pigment is found in the serum, and bilirubin spills over into the urine. This group includes the form named chronic idiopathic jaundice (Dubin and Johnson, 1954), which is conspicuous by the presence of a pigment similar to lipofuscin in the liver cells (cf. Dubin, 1958). Clinical symptoms are fluctuating jaundice, episodes of abdominal pain, nausea, vomiting, enlarged liver and dark urine. Bromsulphalein retention is greatly increased.

A few reports have appeared on a syndrome similar to the Dubin-Johnson syndrome, where the characteristic pigment was missing on examination of the liver tissue (Rotor, Manahan and Florentin, 1948; Schiff, Billing and Oikawa, 1959; Haverback and Wirtschafter, 1960). There are some other small differences in symptomatology from the Dubin-Johnson syndrome. Most important of these are the absence of attacks of abdominal pain and the fact that the gall bladder can be easily seen on oral cholecystography. Only six patients with this syndrome have been described in the literature so far, to our knowledge. This makes it difficult to decide if the observed differences are constant features of this disturbance of bile pigment metabolism or if they are a variation of the pigmented type of chronic idiopathic jaundice.

The patient described here seems to belong to the non-pigmented group and is presented in the hope of further clarifying the picture of this pigmentless type of chronic non-haemolytic jaundice without insufficiency of glucuronide formation.

## Case Report

W.M., a 7-year-old girl, born in 1952, is the only child of a family from southern Switzerland. The family history gives no indication of liver or blood disease; the pregnancy was normal and the child's birth weight was 3,270 g. At the age of 4 weeks the mother observed a yellow tinge in the skin and this slightly icteric appearance has persisted. It is visible especially in the sclerae, but at times it increases in strength to an overt jaundice. When this happens the child is tired and anorrhexic, but there is no abdominal pain. Sometimes during these attacks the stools are paler than normal and the urine is dark. After a few days these symptoms subside. At the age of 13 months and 16 months the girl was seen by a paediatrician who found no abnormalities apart from icteric sclerae. Liver and spleen were not enlarged, Hb was 67% and 76% respectively. At the age of 28 months the patient was admitted to our hospital because of persistent jaundice.

**First Admission.** On admission skin and sclerae were icteric. The liver was palpable one finger-breadth below the costal margin; the spleen was not enlarged.

Haematological studies showed no abnormalities with the exception of a slightly higher proportion of smaller cells than normal in the Price-Jones curve. Several times the fragility to hypotonic saline solutions was a little increased, total haemolysis occurring at from 0·49 to 0·51%. These features were not persistent, however, and on other occasions normal values were observed. The direct Coombs test and indirect antiglobulin tests for antibodies were negative. Serum bilirubin level was high and varied between 7·2 and 4·2 mg. % with a moderate to strong direct van den Bergh reaction. Urobilinogen level in the urine was also high, but surprisingly no bilirubin could be detected in the urine with the method used at that time.

Extra-hepatic obstruction was thought unlikely from the benign course and from the normal aspect of the faeces. Also, on duodenal aspiration, normal enzyme activity (trypsin, diastase and lipase) was present in the duodenal secretion and A, B and C bile of normal appearance and in normal amounts could be aspirated. Other laboratory findings are shown in Table 1.

Because of the slightly increased red cell fragility and spherocytosis a mild form of hereditary spherocytic anaemia was assumed at that time, despite the rather high bilirubin concentration in the serum and the fact that no abnormalities were found in the parents.

**Second Admission.** In 1959, at the age of 7½ years, the patient was readmitted for further studies because of her persistent slight jaundice with occasional exacerbation. On admission the height was 120 cm. and body weight 23·7 kg. There was a reddening of the throat and a throat culture produced haemolytic streptococci. The antistreptolysin titre was 1:320. Otherwise physical examination was negative, except for the icteric sclerae. Liver and spleen could be felt at the costal margin.

TABLE 1
LABORATORY FINDINGS

| Investigations | 1955 | 1959 |
|---|---|---|
| Haemoglobin | 87% | 90% |
| Red cells millions/mm.³ | 4·36 | 4·26 |
| Colour index | 1·0 | 1·07 |
| Anisocytosis | slight | slight |
| Leucocytes per mm.³ | 7,300 | 9,150 |
| Neutrophils stab | 7·5 | 15·5 |
| Neutrophils segmented | 22·5 | 55 |
| Neutrophils eosinophil | — | 0·5 |
| Neutrophils basophil | — | — |
| Monocytes | 12·0 | 5·0 |
| Lymphocytes | 58 | 23·5 |
| Plasma cells | — | 0·5 |
| Reticulocytes % | 3·5 | 1·3 |
| Platelets | 286,000 | 81,000–160,000 |
| Haematocrit % | 43 | — |
| Ratio of red cells to white cells in bone marrow | 26/100 | 12/100 |
| Price-Jones curve | slight shift to left | normal |
| Osmotic fragility: | | |
| beginning of haemolysis | 0·45 to 0·53% | 0·49% |
| total haemolysis | 0·39 to 0·41% | 0·35% |
| Direct Coombs test | negative | negative |
| Indirect antiglobulin test | negative | |
| Auto-antibodies | negative | |
| Wassermann reaction | negative | |
| Prothrombin | 80–100% | 40–100% |
| Coagulation time | 5 min. | 3 min. |
| Bleeding time (sec.) | 45 | 90 |

TABLE 2
LIVER FUNCTION TESTS

| Investigations | 1955 | 1960 |
|---|---|---|
| Serum bilirubin (mg. %) | 4·2–7·2 | 3·7–5·0 |
| Direct | + | 2·2–3·5 |
| Cholesterol (mg. %) | | 177 |
| Esters | | 72% |
| Total protein (g. %) | | 5·3–6·7 |
| Serum iron (μg. %) | 54–86 | 116 |
| Blood sugar (mg. %) | 93 | |
| Serum alkaline phosphatase | | 12 |
| Takata-Ara | (+) | + |
| Cadmium reaction | | trace |
| Thymol turbidity, units | | 2·3 |
| Transaminase: | | |
| SGOT, units | | 29 |
| SGPT, units | | 12 |
| Galactose tolerance | normal | normal |
| 'Bromsulphalein' retention | — | 5% and 4% |
| Hippuric acid test | — | low normal |
| NAPA-test for glucuronide formation | — | normal |
| Urine: | | |
| Urobilinogen | increased | 4·9 mg./24 hrs |
| Bilirubin | | 0·62 mg./24 hrs |
| Coproporphyrin | | trace |
| Melanin | | negative |
| Duodenal fluid: | | |
| Trypsin | normal | normal |
| Diastase | normal | normal |
| Lipase | normal | normal |

BLOOD FINDINGS. The red cell count was 4·26 million, Hb 89% and colour index 1·07. Some anisocytosis was discernible. Reticulocytes 1·3%; white cell count 9,150 per c.mm. The differential count and additional haematological data are listed in Table 1.

LIVER FUNCTION (Table 2). Takata-Ara reaction was one plus; cadmium, a trace; thymol-turbidity 2·3 units; total serum protein 5·35 and 6·7 g. %. Paper electrophoresis revealed albumin 48%, $\alpha_1$-globulin 5·8%, $\alpha_2$ 11·6%, $\beta$ 13·4%, and $\gamma$-globulin 21·2%. The increase in $\gamma$-globulin was probably produced by the existing throat infection. Serum transaminase glutamic oxalacetic, 29 units; glutamic pyruvic, 12 units; serum alkaline phosphatase, 12 units; cholesterol, 177 mg. %; cholesterol esters, 72%. The prothrombin activity was 40% on admission, but afterwards, on repeated determinations, was always normal.

Serum bilirubin determination (methods of Jendrassik and Gróf, 1938; Malloy and Evelyn, 1937) gave values between 5·0 and 4·1 mg. % for total bilirubin, the direct reacting pigment being 3·5 to 2·2 mg. %. Paper chromatography of the serum by the method of Schmid (1957) showed two bands of azoderivatives with an Rf of 0·46 and 0·58.

URINE. Urines generally were rather dark in colour. Urobilinogen excretion (average of two 24-hour collections) amounted to 4·86 mg. per day and therefore was greatly increased (method of Schwartz, Sborov and Watson, 1944). As expected from the increased amount of 'direct' reacting bile pigment in the serum, some bilirubin was excreted in the urine (0·62 mg. per 24 hours) (method of With, 1942). Only a trace of porphyrin was found and a qualitative test for melanin was negative. Amino-nitrogen excretion was normal (31 mg. per 24 hours) and the amino-N-coefficient was 1·7.

STOOLS. The stools were of normal colour. The faecal urobilinogen excretion (average of two 24-hour collections) was 32·25 mg. per day, a value that is normal for this age group (method used for estimation, Schwartz *et al.*, 1944). The total bile pigment excretion (stools and urine) in 24 hours amounted to 37·1 mg. The haemolytic index (calculating a blood volume of 1,900 ml.) was 15. This normal value excluded an accelerated red cell destruction. The ratio of faecal to urinary urobilinogen was very low, 6·6:1 (the normal is about 100:1), showing that a much larger amount of urobilinogen was excreted by the kidneys than is normal.

'BROMSULPHALEIN' TEST. After intravenous injection of a dose of 5 mg. of 'bromsulphalein' (BSP) per kg. body weight, the retention in the blood 30 minutes later was 51%. On repetition of the test five weeks later, it was 48% (normal at this age 0-1·5%). The dye was detectable in the duodenal aspirate 45 minutes after the injection, whereas it normally appears within the first 15 minutes. The peak concentration of 66 mg. % in the duodenal fluid was reached after 70 minutes and two hours after the injection the concentration was still higher than 50 mg. %. Because of the difficulties in recording duodenal fluid volume it is not possible to give figures for absolute amounts excreted. In the urine 14·6% of the injected dose of BSP (125 mg.) was excreted in the first two hours after administration; the following portions contained progressively smaller amounts, but even 18 hours later the BSP concentration was still 1·9 mg. %. The results of the test are shown in Fig. 1. In addition chromatography of BSP metabolites in the serum 15, 30, 120 and 420 minutes after injection by the method of Carbone, Grodsky and Hjelte (1959) gave values of 5·3%, 5·4%, 17% and 26% respectively for BSP conjugates. This indicates an increase in the percentage of conjugated BSP concurring with a decrease in free BSP. In the bile, apart from free BSP, up to three BSP-conjugated were present, with Rf-values of 0·64, 0·57 and 0·40. From these findings an impairment of 'bromsulphalein' excretion is evident which seems to be caused not so much by a deficiency of conjugation as of secretion.

HIPPURIC ACID TEST. After intravenous injection of 1·5 g. benzoic acid the patient excreted 0·59 g. hippuric acid in the urine within the following one-hour period. In our experience this can be considered as a low normal result in a child of this age. Glycine conjugating ability seems not to be impaired to a great extent.

GLUCURONIDE FORMATION. N-acetyl-p-aminophenol (NAPA) was used as a substance to test the ability of the patient to form glucuronides. After oral or intravenous administration this substance is conjugated at the hydroxyl-group and excreted as glucuronide and sulphate in the urine. In adults the recovery within 24 hours is about 70 to 80% of the dose administered. Estimation of free NAPA in the serum and urine (Brodie and Axelrod, 1948) before and after hydrolysis with β-glucuronidase makes it possible to calculate the amount of NAPA conjugated with glucuronic acid (Vest and Streiff, 1959). Fig. 2 shows the results obtained with this test after intravenous injection of 240 mg. of N-acetyl-p-aminophenol. Retention in the serum was 7·6% after six hours (normal values are less than 10%). The curve showing the concentration of NAPA-glucuronide at various time intervals also takes a normal course. The girl excreted in the urine 72·7% of the dose injected within 24 hours. Of this 10·8% was in the free form, 45% conjugated with glucuronic acid and the rest with sulphate. Fig. 2 also shows the increase of glucuronic acid in the serum, which occurred after administration of NAPA. On the other hand this load did not influence the level of the serum bilirubin. The excretion of glucuronic acid (estimated by the method of Dische, 1947) in the urine amounted to 57 mg. per 12 hours during a control period. After the injection of the NAPA it rose to 177 mg. in the first 12-hour period and to 107 mg. in the second. These findings show that glucuronide formation is not deficient in this patient.

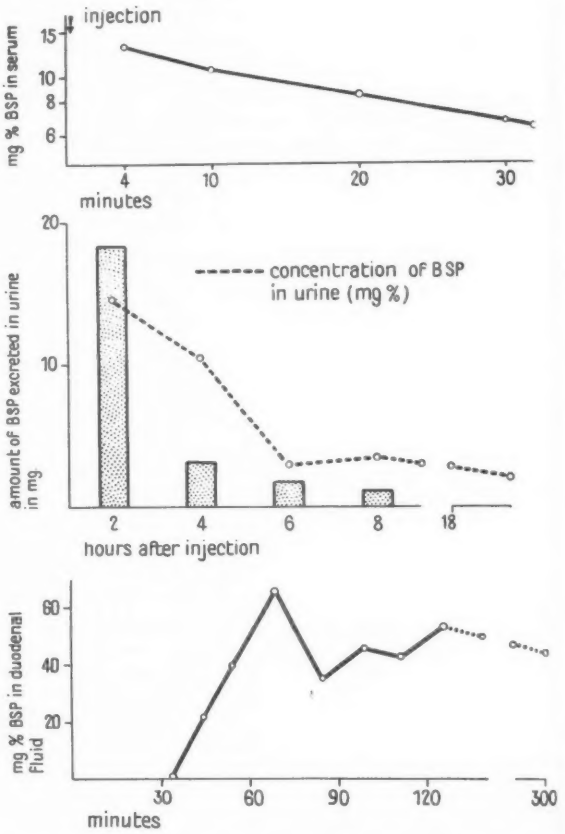


FIG. 1.—Bromsulphalein test; Upper part, concentration of 'bromsulphalein' in the serum after injection of BSP 5 mg. per kg. body weight, retention after 30 minutes, 51%; Middle part, amount of BSP excreted in the urine in four two-hour periods and concentration of BSP in the urine at various intervals after injection; Lower part, time of appearance and concentration of BSP in the duodenal fluid.

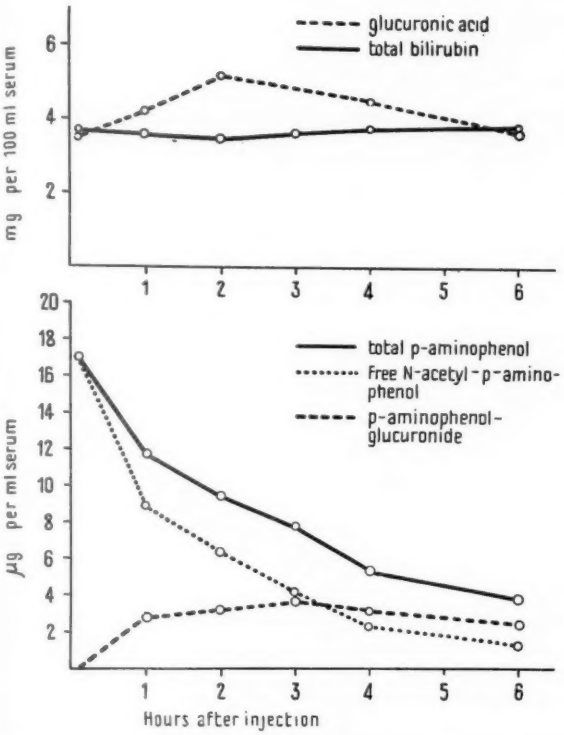


FIG. 2.—Test for the ability of the liver to form glucuronides; Upper part, concentration of glucuronic acid and total bilirubin in the serum at various times after injection of N-acetyl-p-aminophenol in a dose of 10 mg. per kg. body weight; Lower part, concentration of total p-aminophenol, free N-acetyl-p-aminophenol and p-aminophenol-glucuronide in the serum after the NAPA load.

RADIOGRAPHIC EXAMINATION. An oral cholecystography with four tablets of iopanoic acid (Cistobil 'Cilag') showed a well-filled gall bladder shadow. After ingestion of egg-yolk a contraction of the vesicle was clearly visible.

LIVER BIOPSY. A liver biopsy was performed, using a Menghini needle (Menghini, 1958). Histological examination* revealed normal liver tissue with an unaltered lobular hepatic structure. There was no increase in connective tissue in the portal tracts. The small bile ductules were not dilated and there were no bile thrombi in the bile capillaries. Glycogen was present in the liver cells in normal amounts. No abnormal pigmentation was seen either in the liver or in the Kupffer cells.

## Discussion

This patient presented the following symptoms: a chronic jaundice with a serum bilirubin level between 4 and 7 mg. %, 50 to 70% of which reacted directly in the van den Bergh reaction; a normal urobilinogen excretion in the stools but an increased amount of urinary urobilinogen and bilirubinuria; a markedly impaired BSP test, apparently without gross deficiency of conjugation; a low normal hippuric acid test; a normal glucuronide formation in a N-acetyl-p-aminophenol loading test; no evident signs of hepatocellular damage (normal flocculation-tests, normal prothrombin, normal transaminase, etc.), and a liver biopsy showing no alterations.

The absence of anaemia and increased erythropoiesis, the normal amounts of urobilinogen in the stools and the considerable concentration of 'direct' bilirubin in the serum indicate that the icterus is not haemolytic in origin.

An incomplete biliary obstruction should lead to reduced faecal bile pigment. In addition, some signs of liver damage would be expected after an obstruction of this duration, but were not present in this patient. The results of the liver biopsy and the prompt filling of the gall bladder on cholecystography also rule out a biliary obstruction.

Constitutional hepatic dysfunction (Gilbert's disease) can be excluded on the basis of normal glucuronide formation, the occurrence of direct bilirubin in the serum, the bilirubinuria and the abnormal BSP retention.

The case can be differentiated from chronic idiopathic jaundice (Dubin-Johnson; black liver jaundice) by the absence of the characteristic pigment in the liver cells and the filling of the gall bladder on oral cholecystography. The symptom of abdominal pain, so commonly found in the Dubin-Johnson disease, was also missing. It seems likely therefore that this girl belongs to the group of patients with non-haemolytic jaundice with conjugated bilirubin in the serum, first described by Rotor *et al.* (1948), where no pigmentation is present in the liver cells.

In contrast to the observations of Schiff *et al.* (1959) urinary urobilinogen excretion was increased in this patient. This corroborates Haverback and Wirtschafter (1960) who found high urinary urobilinogen levels in their two patients. Increased values of urinary bile pigment have also been found in chronic idiopathic jaundice with liver cell pigmentation (Dubin, 1958).

There is also some discrepancy with the findings of Schiff *et al.* (1959) with regard to the percentage of 'bromsulphalein' conjugates in the serum after BSP injection. They report 6% and 4% respectively at 45 and 90 minutes and we found 5·3% at 15 minutes, 5·4% at 30, 17% at 120 and 26% at 420 minutes. From this it would seem that the percentage of conjugates increases with time.

* Professor F. Roulet performed the examination of the liver biopsy specimen.

Perhaps, as with bilirubin, there is no deficiency of 'bromsulphalein' conjugation but mainly of secretion and this leads to the diminished removal rate from the plasma.

Nothing is known about the nature of the defect in this syndrome. Because an insufficiency of bilirubin glucuronide formation has been ruled out by all investigators, an impairment in the hepatic excretion of bilirubin glucuronide and a diminished uptake of bilirubin by the hepatic cells has been postulated (Schiff *et al.*, 1959). The familial occurrence makes it possible that the defect is a genetic error of metabolism. Males and females can be affected. The condition seems to be compatible with normal life as evidenced by the stationary state of health of Rotor's original patients (Rotor, 1960) more than 12 years after their initial examination.

## Summary

A case of non-haemolytic, chronic jaundice in a girl, 7 years of age, is presented. The pertinent findings were onset of jaundice at 4 weeks of age, serum bilirubin levels between 4 and 7 mg. %, 50 to 70% of which gave a direct reaction, normal urobilinogen excretion in the stools, but increased urinary urobilinogen and bilirubinuria, 'bromsulphalein' retention of 50% after 30 minutes and low normal hippuric acid formation. The ability to conjugate with glucuronic acid in a N-acetyl-p-aminophenol loading test was normal. Oral cholecystography revealed a normal gall bladder. Other liver function tests were essentially normal. Liver biopsy showed a regular structure and appearance of the liver tissue without pigmentation. Chronic idiopathic jaundice (Dubin-Johnson syndrome) could therefore be ruled out and the patient was classified as a case of jaundice of the type described by Rotor *et al.* (1948).

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# ARTERIOVENOUS ANEURYSM OF THE GREAT VEIN OF GALEN WITH HEART FAILURE IN THE NEONATAL PERIOD

BY

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The great cerebral vein of Galen extends from the junction of the two internal cerebral veins under the splenium of the corpus callosum to the commencement of the straight sinus. Arteriovenous aneurysms of this vein are rare congenital anomalies and only 22 cases have been found in a review of the literature.

Other types of cerebral arteriovenous aneurysms are not so unusual. Their true incidence has become more apparent following the widespread use of angiography. Mackenzie (1953) estimated their occurrence as 1% of all neurological admissions. By way of contrast Paterson and McKissock (1956) found no example of great cerebral vein aneurysm in 110 cases of cerebral arteriovenous aneurysm, and the same is true of the series reported by Olivecrona and Riives (1948), Mackenzie (1953) and Potter (1955). These vascular malformations are predominantly of two main types (Hamby, 1952). In the first type, there is a direct end-to-end connexion between an artery and vein, and in the second a network of poorly differentiated, non-capillary vessels intervenes between an artery and several veins, forming a mass of abnormal, dilated and tortuous vessels which sometimes goes by the name of 'angioma' but is not generally considered to be neoplastic. In both types veins not directly involved in the malformation may become enlarged and tortuous in response to the raised venous pressure. The great cerebral vein, however, only shows aneurysmal dilatation when there are one or more abnormal arterial vessels opening into it, its immediate tributaries or continuation. Other vascular malformations of the brain may coexist. These abnormal arterial vessels have arisen, in the described cases, from the posterior cerebral, posterior communicating, callosal and superior cerebellar arteries and from the choroid plexus of the third ventricle.

Local and general effects may be exerted on the cardiovascular system as in other varieties of arteriovenous aneurysm. The general effects may be difficult to detect. They include a variable increase in pulse pressure, tachycardia, apical systolic murmur and evidence of some enlargement of the heart. The literature contains reports of two babies who died of heart failure associated with a cerebral arteriovenous aneurysm not involving the great cerebral vein (Silverman, Breckx, Craig and Nadas, 1955) (Table 2) and three cases associated with an arteriovenous aneurysm of that vein (Table 1, Cases 11, 13 and 14). One of these infants had coarctation of the aorta as well.

The two cases reported here also died of heart failure associated with arteriovenous aneurysm of the great vein of Galen.

### Case Reports

**Case 1.** S.F. was born September 15, 1959, by normal delivery at about 38 weeks' gestation. The birth weight was 2,240 g. and the head circumference was 33 cm. Respiration was established immediately.

Lower rib recession was noted 16 hours after birth and became more severe. The baby's extremities became cyanosed, peripheral pulsations were poor, there was a soft systolic murmur and the liver became enlarged. The respiratory rate rose to 70 per minute. This picture of respiratory distress and early heart failure was complicated by the occurrence of head retraction and opisthotonus 30 hours after birth followed by twitching and frank fits. Fontanelle tension was normal. Blood calcium was normal. Blood glucose levels were persistently low, 23 and 15 mg. % in the first 24 hours and never above 15 mg. % subsequently in spite of hourly glucose feeds. Lumbar puncture showed xanthochromic fluid under moderately increased pressure with 14,700 red and 75 white blood cells per cu. mm.

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24 CASES OF ARTERIOVENOUS ANE[U]RISM OF THE GREAT VEIN OF GALEN

| Author | Case No. | Lesion and Arterial Supply | Presenting Symptom[s] or Sig[n] | Age at Onset |
|---|---|---|---|---|
| Steinheil (1895) | 1 | Left callosal artery; great and one small cerebral vein dilated; sacculated aneurysm on pedicle on great cerebral vein. Associated right frontal vascular malformation | Convulsions; left hemiano[p]ia | Child |
| Jaeger, Forbes and Dandy (1937) Jaeger and Forbes (1946) | 2 | Huge dilated great cerebral vein pressing on aqueduct; large branches off both post. cerebral arteries into small cerebral veins; further vascular malformations | Internal hydroceph.; epis[t]axis, | [1] mths |
| Russell and Nevin (1940) | 3 | Atresia of int. jugular veins. Left post. cerebral artery branch to great cerebral vein; serpentine mass of vessels | Prominent face and neck [v]eins; motor development; [e]xoph cranial bruit | [1] mths |
| Russell and Nevin (1940) | 4 | Sup. callosal art. and post. cerebral arteries, branches to great cerebral vein; aneurysm compressed aqueduct | Hydrocephalus; distended [s]calp | [1] mths |
| Alpers and Forster (1945) | 5 | Choroidal artery and post. cerebral arteries, branches to aneurysm of great cerebral vein | Mental retardation CNS [s]igns; hydrocephalus | [1] yrs |
| Oscherwitz and Davidoff (1947) | 6 | Tumour probably represented aneurysm of great vein of Galen and branches of circle of Willis | Headaches | [1] yrs |
| Lumsden (1947) | 7 | Aneurysm on upper surface of tentorium attached to near great vein of Galen at junction of inf. sagitt. sinus and straight sinus; ? small artery from choroid plexus of 3rd ventricle | Fits; intraventric. and subarach. [h]rhage | [1] mths |
| Boldrey and Miller (1949) | 8 | Branches of post. cerebral artery to aneurysm of great cerebral vein; pulsatile mass of vessels behind right mastoid | Hydrocephalus; dilated face, sca[l]p pulsatile mass behind mastoid; subarach. haemorrhage | [3] mths |
| Boldrey and Miller (1949) | 9 | Post. communic. and post. cerebral arteries connected to great cerebral vein (angiogram) | Swollen face, eye veins; fatiguabl[e] | Birth |
| Wolfe and France (1949) | 10 | 'At least one artery entered aneurysm of great vein of Galen' | Fits; CNS signs; int. hydrocepha[l] | [3] yrs |
| Pollock and Laslett (1953) | 11 | Post. cerebral and sup. cerebral arteries communic. with aneurysm of great vein of Galen and sag. sinus; also vessels from int. cerebral veins, most of supply vessels appeared to be thrombosed | Heart failure; large head | Birth |
| Petit-Dutaillis, Guiot and Berdet (1953) | 12 | Branches of post. cerebral arteries to aneurysm of great vein of Galen | Hydrocephalus | 4 mths |
| Clément, Gerbeaux, Combes-Hamelle, Pertuiset and Petranca (1954) | 13 | Feeding vessels to aneurysm of great cerebral vein not identified; much thrombus | Dyspnoea; increased muscul[ar] dysphagia; cyanotic attacks | ? Birth [10] days |
| Clément *et al.* (1954) | 14 | Post. cerebral arteries communicn with aneurysm of great cerebral vein; also 'very abnormal arterial distribution' | Failure to thrive; wasting; hy[d] dilated veins; cranial bruit; [c] | ? 3 wks |
| Clément *et al.* (1954) | 15 | Personal communication on similar case | No details | Infancy |
| French and Peyton (1954) | 16 | Anterior cerebral artery group communic. with great cerebral vein | Large head; failure to thrive; retardation | 2 mths |
| French and Peyton (1954) | 17 | Abnormal mass of vessels on medial side. Right cerebral hemisphere, communic. with great cerebral vein, ant. callosal artery enlarged | Sub-arach. haemorrhages | ? |
| French and Peyton (1954) | 18 | Arteriovenous malformation near pineal with rapid filling of great vein of Galen; abnormally large ? left ant. cerebral artery | Headache; slurred speech | ? |
| French and Peyton (1954) | 19 | Branches of post. cerebral arteries into much dilated great vein of Galen | Headaches; subarach. haemorrh[a] | ? |
| French and Peyton (1954) | 20 | Enlarged sup. great cerebral artery into large aneurysmal sac near pineal, draining into dilated great vein of Galen | Headaches; photophobia; [l]ethargy; subarach. haemorrh[a]tal illness | ? |
| Hirano and Terry (1958) | 21 | Branches of post. cerebral arteries seemed to end blindly in wall of aneurysm of great cerebral vein | Hydrocephalus, epistaxis, prop[t] pyrexia, ? cause | 5 mths |
| Gibson, *et al.* (1959) | 22 | Branches of post. cerebral artery to aneurysm of great cerebral vein, compressing aqueduct | Hydrocephalus | 6 mths |
| Claireaux and Newman (Case 1) | 23 | Arteriovenous aneurysm of both post. cerebral arteries and great cerebral vein | Heart failure, fits, opisthotonos | 36 hrs |
| Claireaux and Newman (Case 2) | 24 | Arteriovenous aneurysm of right post. cerebral artery and great cerebral vein | Neck retraction | 24 hrs |

[s]:—Nil

HE G EAT CEREBRAL VEIN OF GALEN

| Sig at Onset | Age at Diagnosis | Associated Cardiovascular Signs | Surgery | Outcome |
|---|---|---|---|---|
| Child | 49 yrs | — | — | Died |
| mths | 4 yrs | Murmur and increased cardiac dullness after 'flu at 8 mths; bruit in neck at 27 mths, low blood pressure, anaemia; carotids dilated, also jugulars | Carotid ligation | Died |
| mths | 17 mths | — | — | Died |
| mths | 17 mths | None in life | Decompression | Died |
| yrs | 18 yrs | — | Craniotomy | Died |
| yrs | 27 yrs | Soft blowing systolic murmur | Craniotomy | Alive |
| mths | 7 mths | — | — | Died |
| mths | 16 mths | — | Carotid ligation; clipping of feeding arteries | Alive |
| Birth | 15 yrs | — | Carotid ligation | Alive |
| yrs | 21 yrs | — | Torkildsen's operation | Died |
| Birth | 4 days | Heart failure | — | Died |
| mths | 4 mths | — | — | Alive |
| Birth<br>days | 1 mth | Heart failure | — | Died |
| 3 wks | 7 mths | Heart enlarged; coarctation of aorta | — | Died |
| Infancy | — | — | — | Died |
| mths | 21 mths | — | Craniotomies; clipping of feeding arteries | Alive |
| ? | 12 yrs | — | Clipping of feeding arteries | Alive |
| ? | 22 yrs | — | Clipping of feeding arteries | Alive |
| ? | 14 yrs | — | — | Alive |
| ? | 43 yrs | — | Craniotomy | Alive |
| mths | 28 mths | — | — | Died |
| mth | 4¾ yrs | — | Anastomosis of spinal theca to peritoneum | Died |
| hrs | 4 days | Cyanosis, systolic murmur, neck pulsations, heart failure | — | Died |
| hrs | 16 days | Cyanosis, systolic murmur, neck pulsations | — | Died |

:—Nil not mentioned

TABLE 2

HEART FAILURE ASSOCIATED WITH CEREBRAL ARTERIOVENOUS ANEURYSM NOT INVOLVING GREAT CEREBRAL VEIN OF GALEN

| Author | Case No. | Lesion and Arterial Supply | Presenting Symptoms or Signs | Age at Onset | Age at Diagnosis | Associated Cardiovascular Signs | Surgery | Outcome |
|---|---|---|---|---|---|---|---|---|
| Silverman *et al.* (1955) | 1 | Right cerebral hemisphere almost replaced by massive vascular network penetrating right frontal bone; right middle and post. cerebral arteries gave branches to communicate with dilated sup. sagitt. sinus | Dyspnoea; cyanosis | 4 hrs | 1 day | Systolic murmur; right carotid thrill; cardiac enlargement and failure | — | Died |
| Silverman *et al.* (1955) | 2 | Large cirsoid aneurysm between middle cerebral artery and sigmoid sinus; large tortuous vascular channels | Respiratory distress; cyanosis; shrill cry | 30 hrs | 3 days | Systolic murmur; venous congestion; cardiac enlargement | — | Died |

The cerebrospinal fluid glucose level was 30 mg. %. The opisthotonus improved markedly after the lumbar puncture but relapsed. The fits, some left sided, recurred. Neck pulsations became very vigorous. Venous congestion, further enlargement of the liver and peripheral oedema developed. Digitalization caused only a transient and partial reversal of these signs. An electrocardiogram showed digitalis effect and increased P waves and some evidence of left as well as of right ventricular enlargement. The baby died on the fourth day, in heart failure. Blood glucose levels had shown no sign of rising.

ELECTROENCEPHALOGRAM. 'The pattern of this record is that of a full term normal baby when awake and sleeping. There is perhaps a little more rhythmic activity at 15 c./sec. than usual but this may be accounted for by the prematurity. This activity is mostly seen when the baby is awake and is up to 25 μV in amplitude. When the baby is asleep there are repeated single or multiphasic sharp waves up to 250 μV in amplitude and up to duration 0·5 sec. These slow sharp waves are unilateral and occur simultaneously over all areas of the head and about equally on both sides' (Dr. Ruth Harris).

RADIOLOGY. Skull radiograph revealed no abnormality; chest radiograph showed only moderate cardiac enlargement.

NECROPSY. The body was that of a small male infant weighing 2,150 g. The dura mater and pia arachnoid were healthy. The brain (333 g.) was firm. The torcular Herophili was greatly enlarged and contained firm clot. Clot was also present in the superior and inferior longitudinal sinuses, the transverse sinuses and the jugular bulbs. The jugular veins appeared to be normal. At the base of the brain a large aneurysm was found. This was largely composed of a grossly distended great cerebral vein of Galen which communicated anteriorly with both posterior cerebral arteries and posteriorly with the distended torcular (Fig. 1). The aneurysmal sac measured 2·2 × 1·5 cm. The arterial communication was complex. The basilar artery divided anteriorly into the right and left posterior cerebral arteries in the usual manner. The right posterior cerebral artery then divided immediately into four and these reunited after passing downwards and backwards for a distance of 3 cm. The thick vessel thus formed then subdivided again before uniting with the aneurysm (Fig. 2). The left posterior cerebral artery divided into three and the branches joined the anterior part of the aneurysm. The great cerebral vein after receiving the internal cerebral veins expanded into a thick-walled sac. This sac received both posterior cerebral arteries and these passed backwards to join the torcular Herophili. The aneurysm had a bulbous anterior portion, a narrow neck and a fusiform body. The cerebral veins were not distended. The lower portion of the

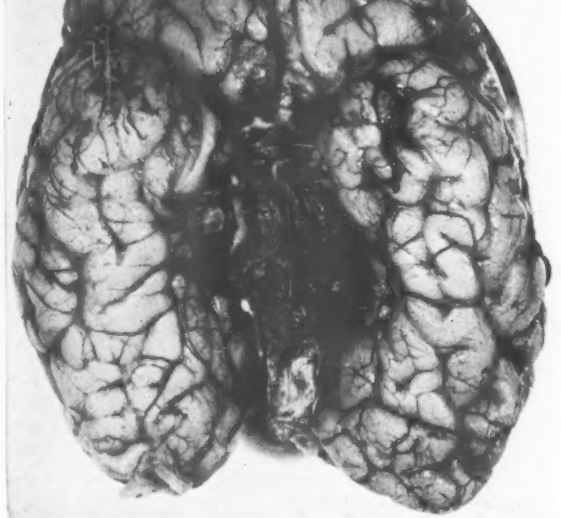

FIG. 1.—Case 1, brain; the inferior surface is exposed to show the aneurysm of the great cerebral vein and the abnormal communications with the posterior cerebral arteries.

aqueduct of Sylvius was of normal calibre and the fourth ventricle was not distended. The anterior surface of the cerebellum was hollowed in the region of the aneurysm. The brain was congested.

The pericardium was clear and glistening and there was a moderate quantity of clear, yellow fluid in the pericardial sac. The heart was enlarged as a result of dilatation of the right atrium and right ventricle. Both chambers contained a large amount of blood clot. The foramen ovale and ductus arteriosus were patent. The valves and great vessels had a normal appearance.

The larynx, trachea and bronchi were healthy. The lungs were congested and some subpleural haemorrhages were present. On slicing a few haemorrhagic areas were noted. The stomach and bowel were healthy. The liver (52 g.) and spleen (5 g.) were not enlarged. The genito-urinary tract was healthy and the endocrine glands showed no abnormality. Supernumerary digits were present on the lateral border of each hand. There was a complete extra finger on the left hand and a rudimentary one on the right. The fifth toe of the right foot was bifid.

HISTOLOGY.

*Lungs.* The pleura was healthy. The lungs were congested but quite well expanded. Some patchy haemorrhage was present. In some areas the alveolar ducts and alveoli were flooded with red cells. The bronchi were healthy. There was no pneumonia.

*Aneurysm.* A section was taken through the most dilated portion of the great cerebral vein. The lumen contained fibrin thrombus. The wall was quite thin and there was evidence of degeneration. No intima was recognized.

*Left Posterior Cerebral Artery.* The lumen was occluded by fresh thrombus which showed no evidence of organization. The vessel was distended as a result of the enclosed thrombus. The wall showed no degenerative change.

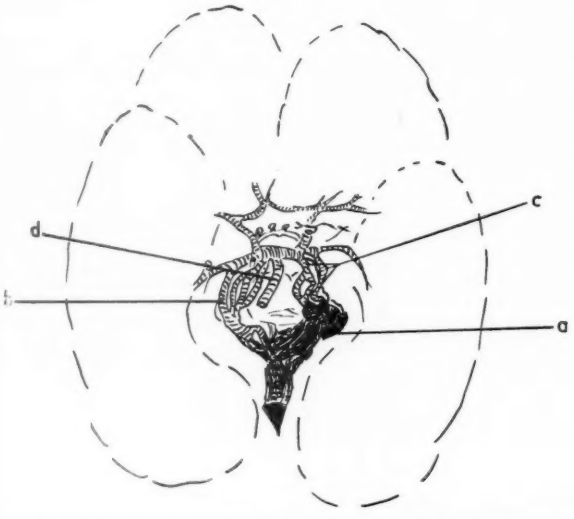


FIG. 2.—Case 1, brain; outline drawing to show (*a*) aneurysm of great cerebral vein, (*b*) right posterior cerebral artery with abnormal branching, (*c*) left posterior cerebral artery, (*d*) basilar artery.

SUMMARY. Cerebral arteriovenous aneurysm; intrapulmonary haemorrhage; supernumerary digits on each hand and bifid right fifth toe.

**Case 2.** The mother, 23 years of age, para 0 had bilateral active tuberculosis and during pregnancy had to be treated for pyelonephritis resulting from infection with *Escherichia coli.* She went into labour at term and the infant was delivered spontaneously. The first stage of labour lasted 18 hours 30 minutes and the second stage 30 minutes. There was a vertex presentation.

The infant was a male and weighed 3,715 g. at birth. The head circumference was 32·5 cm. The infant's condition was good and he cried immediately. There was no peripheral cyanosis but cardiac pulsation was noted to be vigorous and there was strong arterial pulsation in the neck. A systolic murmur was heard over the apex. On radiological examination the heart was seen to be enlarged. One week after birth cyanosis was observed and there was slight pitting oedema of the feet and legs. The pulse rate was 160 per minute and respirations 40 per minute. A diagnosis of congenital malformation of the heart was made. Further radiological examination on the 11th day showed an increase in the size of the heart. Cyanosis became more marked and neck retraction was noted. The infant's condition steadily deteriorated and he died 16 days after delivery.

NECROPSY. The body was that of a well developed male infant and weighed 3,345 g. The sternum was prominent. The falx and tentorium were intact. The brain (400 g.) was very soft and markedly congested. The great cerebral vein was replaced by a large saccular aneurysm 4·5 cm. in length and 2 cm. in diameter. This aneurysm was attached to the junction of the falx with the tentorium. It communicated anteriorly with the right and left internal cerebral veins and with the right posterior cerebral artery. The cerebral veins were engorged but not thrombosed. There was slight dilatation of the lateral ventricles and of the third ventricle which contained clear cerebrospinal fluid. The aqueduct was patent and the fourth ventricle was of normal size. A small amount of subarachnoid haemorrhage was present over the cerebellum. On slicing the aneurysmal dilatation of the great cerebral vein was found to contain organized thrombus.

The pericardium was clear and glistening, there was a small quantity of clear, straw-coloured fluid in the pericardial sac. The heart was considerably enlarged, chiefly as a result of hypertrophy and dilatation of the right atrium and right ventricle. The interventricular septum was intact and very broad. Thick post-mortem clot was present in the right atrium. There was no structural abnormality of the heart valves or of the great vessels. The foramen ovale was closed. The ductus

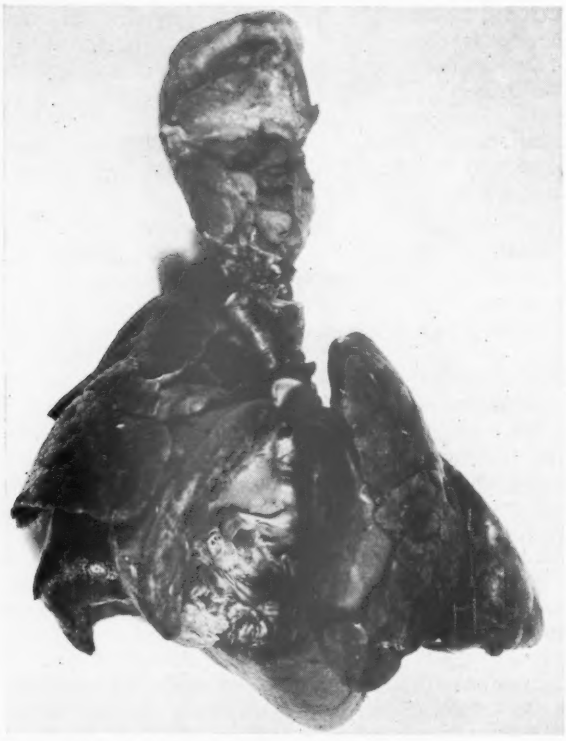

FIG. 3.—Case 2, heart; right ventricle opened to show gross myocardial hypertrophy.

arteriosus was narrowly patent. The venous drainage was normal (Fig. 3).

The larynx, trachea and bronchi were healthy. The lungs were moderately well expanded and congested. Some patchy basal consolidation was found.

The stomach and bowel showed no pathological change. The liver (149 g.) was enlarged and congested. The spleen (15 g.) was large and very congested. The genito-urinary tract was healthy. The endocrine glands showed no abnormality.

HISTOLOGY.

*Lungs.* The pleura was healthy. The lungs were congested and some haemorrhage had occurred into the alveoli. In sections from the lower lobes there were widespread areas of consolidation. Many alveoli and alveolar ducts contained a dense cellular exudate composed of polymorphonuclear leucocytes and histiocytes. Some small bronchi contained a similar exudate. Immediately beyond the consolidated areas there was a zone of overdistension of alveoli and alveolar ducts. The appearance was that of a bronchopneumonia.

SUMMARY. Arteriovenous aneurysm of great cerebral vein; hypertrophy and dilatation of the heart, and terminal bronchopneumonia.

## Discussion

Aneurysm of the great vein of Galen differs clinically from the more common types of cerebral arteriovenous aneurysm in the early onset of symptoms and the apparently greater frequency of serious cardiovascular effect. Moreover, hydrocephalus is a commonly associated feature probably as a result of pressure by the aneurysm on the aqueduct of Sylvius. Hydrocephalus was not present in either of our patients. This is probably the result of the comparatively short duration of any pressure effects. In both the brains we examined, the aqueduct was still widely patent although slightly distorted. Similarly, we found no thickening of the wall of the aneurysm and no evidence of mucinous degeneration such as was reported by Russell and Nevin (1940). This lack of degenerative change appears to indicate that the dilatation of the vein is not secondary to a degeneration of the vessel wall as these workers suggested. In some instances (Russell and Nevin (1940), Case 1) a genuine arteriovenous aneurysm and a vascular hamartoma are present together. In our Case 1 there was some very peculiar branching of each posterior cerebral artery before union with the great cerebral vein took place, but in neither case was there any evidence of a network of fine vessels which might be designated a hamartoma.

In the 24 cases listed (Table 1) symptoms had commenced in infancy or childhood in two, at less than 6 months in 12, at 6 months to 1 year in three, at 1 to 10 years in two and in adult life in only one case. The date of onset was not stated in four cases who were diagnosed at 12, 14, 22 and 43 years respectively. In the more usual type of cerebral arteriovenous aneurysm or 'angioma' symptoms are more usually delayed until the second decade or later (Olivecrona and Riives, 1948; McKissock, 1950; Mackenzie, 1953). Cases presenting in infancy or childhood are proportionately rare.

In great cerebral vein aneurysms the symptomatology includes dilated face and scalp veins, proptosis, fits, headache, the effects of subarachnoid and intraventricular haemorrhage, mental retardation, focal signs in the central nervous system and failure to thrive. General circulatory effects were noted in six of the 24 cases and heart failure appeared to be the primary cause of death in five of these. One had coexisting coarctation of the aorta. Hydrocephalus developed in nine cases, two more having a 'large head'.

The course at first sight appears to be short. Death occurred under the age of 2 in nine, under the age of 5 in three and at 18, 21 and 49 years in a further three. Only one of seven cases reported before 1947 and before angiography was performed for diagnosis was alive at the time of reporting. This contrasts with eight of the remaining patients

and suggests that the prognosis may not really be so gloomy. Death was associated with internal hydrocephalus, fits, haemorrhage, craniotomy and heart failure.

Diagnosis was made by angiography, at necropsy or at operation. An intracranial bruit was not listened for in the two cases reported here and, when sought in other cases, has only sometimes been detected. The association of local or general cardiovascular abnormalities with a suspected intracranial lesion is characteristic of these malformations. The retinal veins appeared normal in the two cases described here.

Treatment is medical and surgical. The former has little to offer. It cannot influence the aneurysm nor the shunt, and the treatment of associated heart failure has been quite unsuccessful. Surgery has had some successes. It was carried out in 10 cases. Carotid ligation, attempts to relieve hydrocephalus and simple craniotomy had poor results. Surviving patients had undergone the following procedures: Craniotomy only, two; carotid ligation, one; carotid ligation with subsequent clipping of arteries feeding the aneurysm, one; clipping of feeding arteries, three. French and Peyton (1954) consider the condition operable if the arterial supply to the aneurysm can be demonstrated by angiography. Occlusion of the feeding arteries (which appears to have taken place spontaneously in Case 21) may not influence associated hydrocephalus, but will probably prevent pressure effects from further enlargement. It must also reduce the likelihood of haemorrhage and should correct the effects of the shunt on the cerebral circulation and on the heart itself. The youngest patients in whom feeding arteries were clipped were both under 2 years of age. Both survived but neither had been in heart failure. It is doubtful whether any of the infants who died of this complication could have been saved, but it is just possible that carotid occlusion might have improved their circulatory status temporarily.

The cardiovascular effects associated with arteriovenous aneurysms may be extensive. They have been reviewed by Lewis and Drury (1923), Holman (1923, 1924), Reid (1925a, b), McGuire (1935) and Potter (1955). Several authors had noted cardiac enlargement in cases of cerebral arteriovenous aneurysm, but Schmitt (1920) appears to be the first to have stressed this feature. He wrote: 'Hypertrophy of the left ventricle . . . is often found in the more advanced stages of cerebral arteriovenous aneurysm' and 'the combination of brain disorder with cardiovascular symptoms is very important in the diagnosis of cerebral arteriovenous aneurysm'. He further mentions the dilatation of arteries to the head. In subsequent accounts the effects on the cardiovascular system are not always mentioned. Their incidence is therefore difficult to assess. Cushing and Bailey (1928) and Dandy (1928) found definite cardiac enlargement lacking in their cases even though it might have been expected in some on the grounds of size of aneurysm, location and duration of symptoms. Brock and Dyke (1932) found cardiac enlargement in four of five cases of cerebral arteriovenous 'angioma'. Ray (1941) noted partly reversible cardiac enlargement in one of 16 cases. Shenkin, Spitz, Grant and Kety (1948) found it in two cases investigated to determine the cerebral blood flow, which was much increased. Silverman *et al.* (1955) record two infants who died in heart failure from this cause in the newborn period and Paterson and McKissock (1956) noted cardiac enlargement in nine of their series of 110 cases. Aneurysm of the great vein of Galen does not feature in these reports but enlargement has occurred in four reported cases, three of whom died in heart failure, as did the two additional babies reported here. The very marked effect on the cardiovascular system exerted by the arteriovenous shunt is indicated in Case 2 where there is enormous hypertrophy of the wall of the right ventricle which was three times the normal thickness for this stage of development.

Hypoglycaemia has not been previously described in this context. It may have been coincidental, but the proximity of the aneurysm to the floor of the fourth ventricle is suggestive.

The cases presented here and the review of the literature make it apparent that cerebral arteriovenous aneurysms may present with symptoms referable to the cardiovascular system. The possibility of such lesions should be considered when a vigorous cardiac impulse and increased neck pulsations are associated with signs of meningeal irritation or convulsions. Respiratory distress may mask these features in the newborn period. If it is possible to confirm the diagnosis by angiography, surgery may offer a chance of successful treatment. Untreated, the patient may die in the newborn period from cardiac failure, or subsequently from the effects of hydrocephalus and haemorrhage.

**Summary**

Two cases of arteriovenous aneurysm of the great vein of Galen are reported. Both were infants who died in the newborn period of heart failure. Both exhibited neck rigidity in addition to cardiovascular signs. One infant had persistent hypo-

# THE SIGNIFICANCE OF INTIMAL THICKENING IN THE ARTERIES OF THE NEWBORN

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From both Europe and North America there have been a number of reports describing the presence of cushion-like areas of intimal thickening and elastic reduplication in the arteries of foetuses and infants (Dock, 1946; Fangman and Hellwig, 1947; Levene, 1956; Robertson, 1960a). The significance of these intimal cushions is uncertain. They are believed by some to be pathological in nature and the early lesions of atherosclerosis. Another view regards them as being a physiological adaptation of the vessel wall to mechanical stress and as having little influence in dictating the later development of atherosclerosis.

At Ibadan, coronary occlusion is rarely seen in the adult African and in the literature there are many reports indicating that atherosclerosis, certainly of the aorta and coronary arteries, is much less severe and extensive in the African Bantu and Negro than in Europeans (Davies, 1948; Edington, 1954; Hannah, 1958; and others). The present investigation sets out to determine whether intimal thickenings occur in the arteries of the African newborn and to compare their incidence with that found in European and North American subjects.

## Methods

The popliteal artery of one leg was examined in 52 newborn African infants, 32 of whom were male and 20 female. Their ages ranged from foetuses of 30 weeks gestation to babies 2 weeks old. Most, however, were full-term stillbirths. In 30 of the cases, 19 male and 11 female, the proximal parts of the anterior descending and circumflex branches of the left coronary artery were also examined. From each vessel a small segment was taken and after fixation in formalin, paraffin sections were prepared and stained by haematoxylin and eosin and Weigert's elastic tissue stain counter-stained by van Gieson.

## Findings

In the newborn the intima of the muscular arteries consists of an elastic membrane, the internal elastic lamina, which is covered by the endothelium. The circular muscle of the media surrounds the intima and is bounded on its outer aspect by the adventitia. Of the 52 popliteal arteries examined, 42 (27 male and 15 female) showed areas in which there was a disturbance of this architecture. The pattern of this varied, but in most instances both the intima and media were affected to form a local cushion-like thickening of the wall. In the intima there occurred a reduplication of the internal elastic lamina so that several coarse lamellae or sometimes numerous fine elastic filaments were formed between which smooth muscle cells could be seen (Fig. 1). In the underlying media bundles of longitudinally orientated muscle also contributed to the thickening

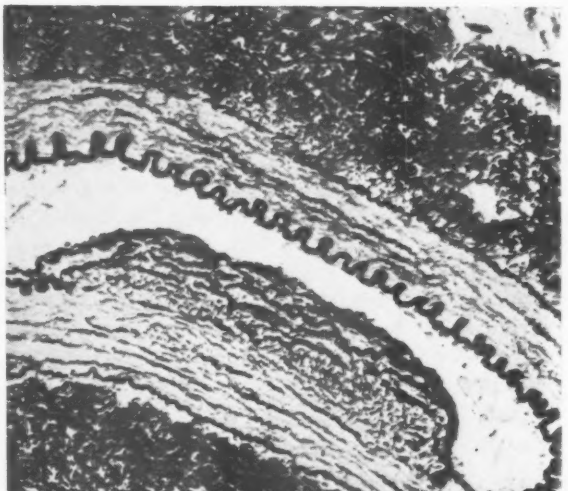

FIG. 1.—Popliteal artery. Full term stillbirth. A cushion-like thickening of the wall is present over which there is reduplication of the internal elastica. (Weigert × 150.)

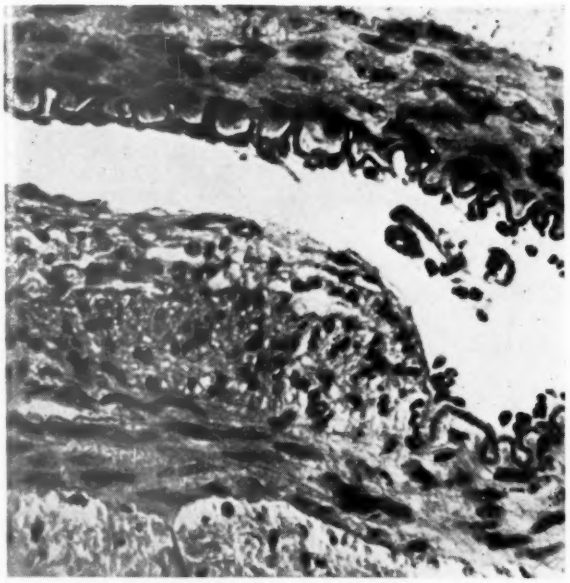

FIG. 2.—High power field of the cushion illustrated in Fig. 1. A band of longitudinal muscle is present in the media beneath the split elastica. (H. and E. × 300.)

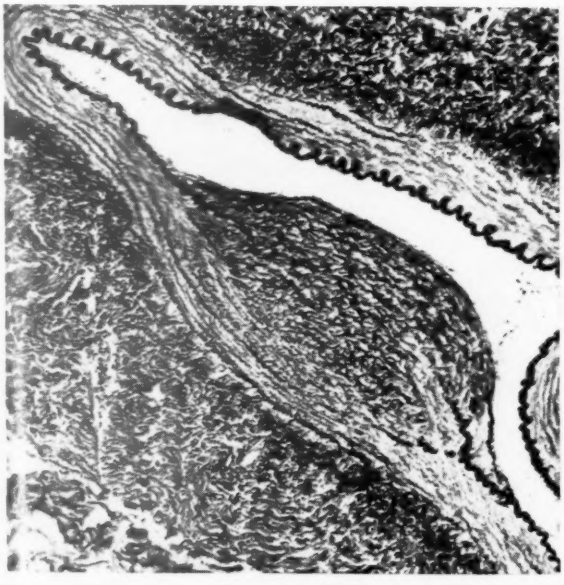

FIG. 3.—Popliteal artery. Full term stillbirth. A cushion showing marked reduplication of the internal elastica. The interstices of the elastic mesh contain many longitudinally orientated muscle cells. (Weigert × 86.)

of the wall (Fig. 2). These longitudinal muscle bundles were the most conspicuous feature of many cushions and in some instances they formed the whole of the thickening, there being no reduplication of the internal elastica. Both the size and complexity of the cushions varied widely, ranging from small nodes of longitudinal muscle in the media to the formation of large musculo-elastic mounds (Fig. 3). They occurred especially at the margins and opposite the mouths of branches, but were apparently not restricted to these sites, although serial sections would have been required to confirm this.

The left coronary artery was examined in 30 subjects and in 16 of these (11 male and five female) cushion-like thickenings of the wall similar to those of the popliteal artery were found. In the coronary vessels reduplication of the internal elastica tended to be more prominent than bundles of longitudinal medial muscle in the formation of the cushions. Only very occasionally, however, did a thickening show no evidence of a medial component. In both the coronary and popliteal vessels the van Gieson stain revealed strands of fibrous tissue in some of the cushions. It was generally associated with the elastic fibrils of the intima. In no instance was it present in large amount and many cushions showed no evidence of a fibrous component.

## Discussion

Two views exist as to the significance of intimal thickenings in the vessels of the newborn. Fangman and Hellwig (1947) and Levene (1956) considered those in the coronary arteries to be pathological and the earliest lesions of atherosclerosis. Dock (1946) and Robertson (1960a) on the other hand, believed that they represented a response of the vessel wall to mechanical stress. In the coronary vessels Dock attributed this stress to the changing length to which these vessels had to adapt themselves during cardiac systole. Robertson, however, described similar thickenings in the popliteal and brachial arteries of the foetus and considered that their function was to buffer a stress due to tugging at the margins of branches and other points of fixation of the vessel during its elongation with pulsation. It was believed that the presence of intimal cushions was of no significance in determining the later development of atherosclerosis, although, if the disease did occur, it tended to localize in these regions of stress (Robertson, 1960b).

In the present study of newborn African subjects, cushion-like thickenings were found in the popliteal and coronary arteries of 81 and 53% of cases respectively. In both vessels the incidence was slightly higher in males than females. From these findings it appears that intimal thickenings occur just as frequently in the newborn of the African Negro as in those of the white races. Thus,

in a series of European foetuses, exactly similar structural changes were found in the popliteal artery of 76% of subjects (Robertson, 1960a) while, in North America, Fangman and Hellwig found coronary thickenings in 12 (40%) of 30 newborn infants, the incidence being higher in males than females. Despite the similar findings in the newborn of both races, most authors are agreed that atherosclerosis is less marked in the African Bantu and Negro than in Europeans. Higginson and Pepler (1954), for example, have found that only 3% of African compared with 32% of Danish subjects of the fourth decade have severe coronary and aortic lesions. The results of the present study therefore support the view that the presence of intimal cushions in the vessels of the newborn plays little part in determining the later development of atherosclerosis.

## Summary

The presence of areas of intimal thickening and elastic reduplication in the popliteal and coronary arteries of newborn African infants is described. Their incidence was found to be similar to that in the newborn of European and North American subjects. The significance of these thickenings in the pathogenesis of atherosclerosis is briefly discussed.

I wish to thank Professor G. M. Edington for his advice and encouragement during the course of this work.

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# HISTIOCYTIC MEDULLARY RETICULOSIS IN A CHILD

BY

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Scott and Robb-Smith (1939), using the name 'histiocytic medullary reticulosis', reported four cases of a subacute illness characterized by fever, anaemia, leucopenia, jaundice and enlargement of the lymph nodes, spleen and liver. Microscopically there was a proliferation of phagocytes and giant cells in the reticulo-endothelial system, the affected tissues showing a tendency to undergo haemorrhage and necrosis. Marshall (1956a, b) described eight cases and referred to seven others reported in the literature since 1939.

The disease has not been reported in children and it is for this reason that the following case is mainly of interest. (For a review of the literature and discussion of various aspects of the disease Marshall's publications, 1956a, 1956b, should be consulted.)

## Case Report

The patient was admitted to the Adelaide Children's Hospital on October 9, 1954, at the age of 4 years 5 months with generalized enlargement of the lymph nodes.

Her previous health had been good, apart from chickenpox and tonsillectomy, until three months before admission when a small lump in the right side of the neck had been noticed by her parents. A month before admission, because of a sudden increase in size of her neck, she was taken to a general practitioner who found rubbery enlargement of five or six lymph nodes in the right side of the neck. He could not feel the spleen at this time. Following treatment with antibiotics the nodes subsided considerably. Two days before admission they enlarged again, accompanied by a fever with a temperature of 102° F., tiredness and loss of appetite.

On admission to hospital the cervical, axillary and inguinal glands were all enlarged and the spleen was felt 3 fingers' breadth below the costal margin. The liver could not be felt. Blood examination showed Hb 10 g./100 ml., the red blood cells numbered 3,800,000 per c.mm. and the white cells 8,800 per c.mm., 61% being neutrophils, 37% lymphocytes and 2% large lymphocytes. No abnormality was seen in a radiograph of the chest. A week after admission the Paul-Bunnell test gave agglutination at a serum dilution of 1 in 32, rising to 1 in 64 three days later. Another blood examination on the day she left hospital, 11 days after her admission, showed Hb 12 g./100 ml., a white cell count of 14,800 per c.mm. of which 45% were neutrophils, 35% lymphocytes, 18% monocytes and 2% abnormal lymphocytes. Apart from two short bursts of fever, up to 100° F., her temperature was normal during her stay. On discharge from hospital her spleen could just be felt at the costal margin and the lymph nodes were much smaller. She was sent home to rest in bed, diagnosed as suffering from infectious mononucleosis.

On November 11, 1954, she returned to hospital with enlargement of the cervical lymph nodes which had apparently occurred over a few hours. Some fever had been noted five days before.

On examination she was pale and had very large fleshy lymph nodes in the right cervical region extending from behind the ear to the supraclavicular fossa. There was also enlargement of the nodes in the right axilla. The left cervical nodes were only slightly enlarged and no enlargement was felt in the inguinal regions. The spleen was enlarged to the level of the umbilicus but the liver could not be felt. The throat and middle ears were not inflamed.

Blood examination soon after admission showed Hb 10 g./100 ml. and a white cell count of 8,200 per c.mm.; bone marrow smears were normal. Further blood examinations during her illness showed a progressive fall in red and white cells and a later fall in platelets; Fig. 1 shows some of these changes. Reticulocytes never made up more than 2% except on one occasion when they reached 4% of the total red cell count. Four days after admission the lymph nodes were smaller but one from the right side of the neck was removed. Microscopical examination revealed that the general architecture of the node had been destroyed apart from some remaining cortical lymphoid follicles. In one part of the cortex was a wedge-shaped area of fibrosis containing scattered plasma cells. Elsewhere there was a mixed population of lymphocytes and plasma cells in an inconspicuous mesh of reticular cells, amongst which were scattered large, sometimes binucleated, mirror-imaged 'reticulum' cells. Reticulin fibrils were increased.

Fever began on November 22, the temperature remaining between 100° and 104° F., with rare falls to normal, until her death. No infective cause for this was found.

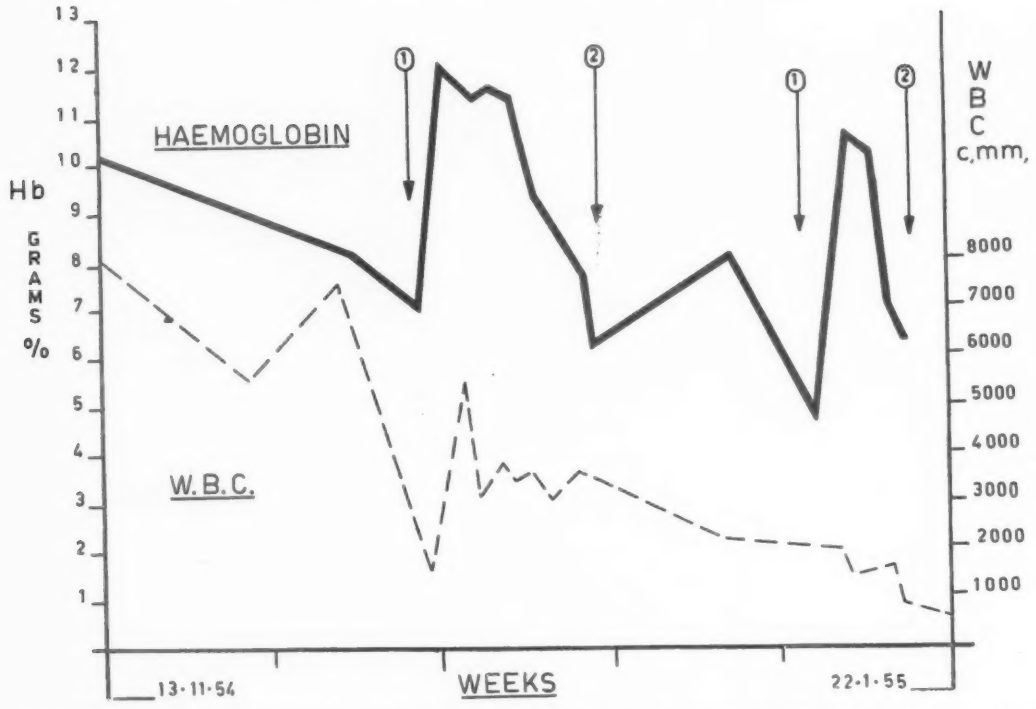


FIG. 1.—Haemoglobin and white count during final hospitalization. The numbered arrows indicate pints of transfused blood.

Blood cultures were negative and her serum did not agglutinate suspensions of *Salmonella* or *Brucella* organisms. In spite of the fever the lymph nodes and spleen began to subside on December 2, the spleen being just palpable by December 9, and the lymph nodes very small. A further aspirate of bone marrow on December 13, contained 27% monocyte-like forms, 13% lymphocytes, 41% polymorphonuclear white cells (with no excess of blast forms), 18% normoblasts and 1% plasma cells. Many of the monocytic forms had ingested red blood corpuscles, normoblasts, neutrophils and platelets (Fig. 2). A platelet count at this time was 120,000 per c.mm. A mild jaundice was noticed on December 22, and this increased steadily. By January 10, 1955, she was extremely wasted and deeply jaundiced; the lymph nodes had again enlarged to the size of marbles and the spleen and liver were easily felt. On January 13, a month since the last platelet count, the number had fallen to 14,000 per c.mm. and did not rise above this level again. At this time purpura and bruising appeared, followed by epistaxes and bleeding from injection sites. A direct Coombs test and a test of red cell fragility, both giving negative results, were not done until a few days before death, which occurred on January 21, 1955.

**Findings at Necropsy.** The autopsy (A.C.H. No. 8/55) was performed 60 hours after death. The body was extremely emaciated, deeply jaundiced, with numerous petechial haemorrhages in the skin. The pleural and abdominal cavities contained clear orange effusions. The enlargement of the lymph nodes involved all groups, the cervical and axillary glands being most affected and the lower abdominal and inguinal nodes least. The cut surfaces of the glands were firm, pink to brownish purple with ill-defined yellow areas of necrosis. A few nodes were uniformly yellowish. The greatly enlarged spleen weighed 260 g., the serosal and cut surfaces showing irregular shaped yellowish areas up to 0·5 cm. in diameter, scattered over a dark purple background. The liver was enlarged and pale fawn, weighing 670 g. The sternal marrow was pale. The lateral muscles of the right thigh were soft and greyish, the overlying subcutaneous tissue haemorrhagic and the skin vesiculated, these changes being considered due to haemorrhage and infection at the site of injections. Both middle ears, but particularly the right, contained greenish pus from which a *Proteus* organism was isolated. Other organs showed no abnormalities apart from the effects of jaundice and anaemia.

Microscopically, identical changes were found in the lymph nodes and spleen. The architecture of the organs was largely replaced by a loose-textured moderately cellular tissue in which there was much haemorrhage and coagulation necrosis. The necrotic areas, particularly in the spleen, resembled small infarcts. The cellular areas consisted of a loose apparently syncytial proliferation of reticular cells, having oval vesicular nuclei and eosinophilic cytoplasm. Amongst this were typical macrophages which varied in number from place to place and many of which contained red cells and nuclear debris (Fig. 3). Another conspicuous but less numerous element was a giant cell having a large and

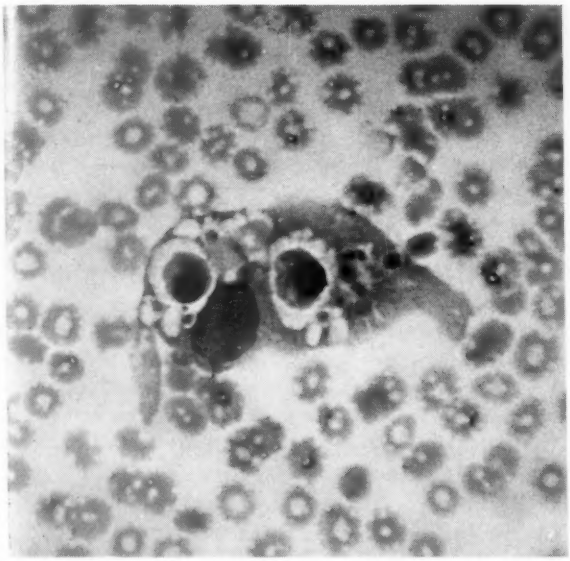

FIG. 2.—Bone marrow smear, showing a large phagocyte containing two red blood corpuscles, two normoblasts and platelets. (Giemsa ×750.)

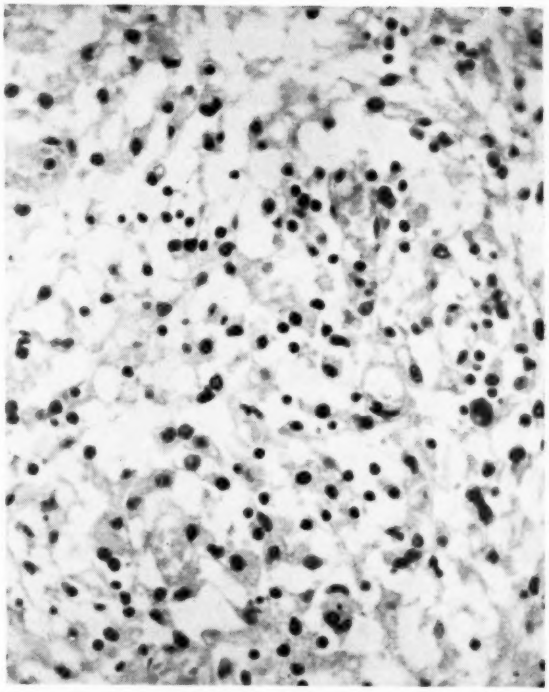

FIG. 3.—Lymph node, showing reticular arrangement of histiocytes. (H. and E. ×330.)

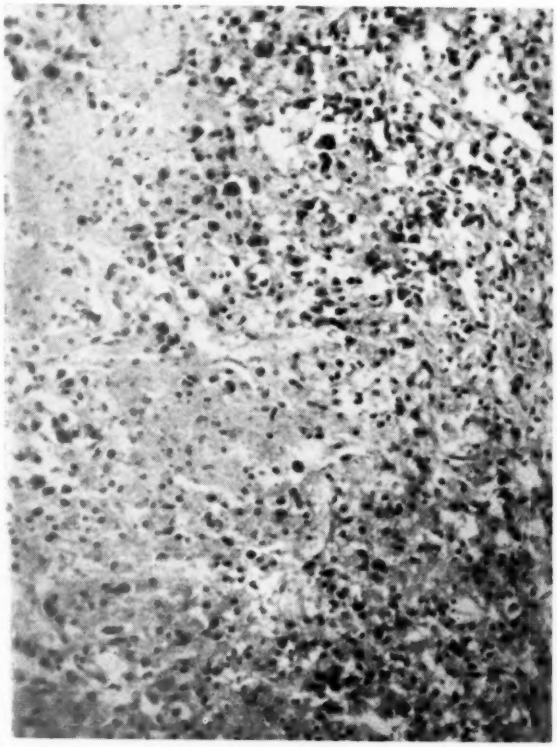

FIG. 4.—Lymph node, showing necrotic areas and densely staining giant cells. (H. and E. ×150.)

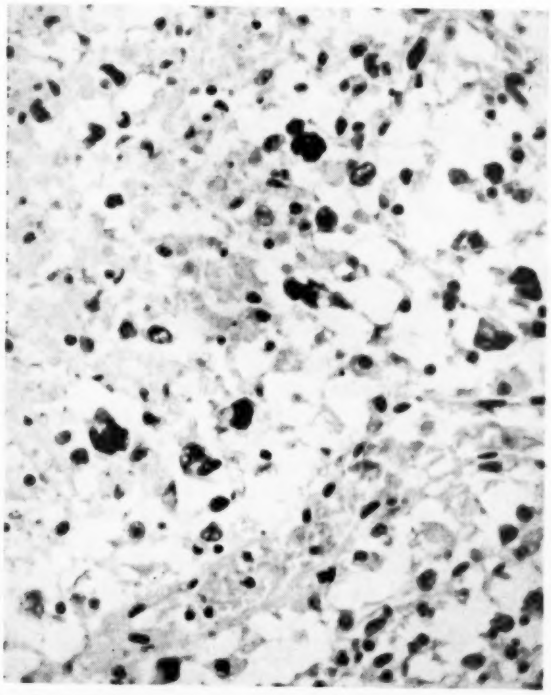

FIG. 5.—Lymph node, showing the irregular-shaped hyperchromatic nuclei of the giant cells. (H. and E. ×330.)

hyperchromatic nucleus and a small amount of eosinophilic or occasionally basophilic cytoplasm (Fig. 4). The nucleus of the cell was commonly irregularly notched or folded, and if, as sometimes occurred, several nuclei were present these were closely packed together and unequal in size (Fig. 5). Transitions between these three main types of cell could be seen. Phagocytosis by the giant cells was not observed. Moderate numbers of mitotic figures were found, mostly in large cells. Mixed with this meshwork of histiocytic cells were small numbers of lymphocytes and many plasma cells and plasmablasts. A notable feature of the abnormal tissue was the large number of thin-walled blood vessels. In the lymph nodes the peripheral sinuses were usually preserved and contained many macrophages. In the spleen a few lymphoid follicles remained.

The sternal marrow showed almost complete replacement by tissue similar to that in the spleen and lymph nodes, except that giant cells were rare.

The liver had undergone a moderate degree of fatty change and congestion, and in addition contained occasional small haemorrhagic and necrotic foci of histiocytes and giant cells. Similar groups of tumour cells were found in the suprarenal cortex. Phagocytosis of red cells by Kupffer cells was present throughout the liver.

Other organs contained no significant changes. Perl's stain for iron revealed much haemosiderin in the spleen and Kupffer cells, but very little in the lymph nodes. Reticulin fibrils were increased in the lymph nodes.

## Discussion

The clinical and pathological findings in this case conform in every way to the previous descriptions of the disease, except for the age of the patient. It is not proposed here to discuss the relation of this condition to other reticuloses; the pathological findings in the reticulo-endothelial organs are, however, quite singular. Nevertheless, the histological changes in the cervical lymph gland of the present case were considered by several pathologists to be typical of classical Hodgkin's disease, appearances which were to be completely replaced by the time of death two months later.

The relapsing nature of the illness also calls for attention, indicating that the course of the disease cannot be fully explained by neoplastic proliferation. The sudden enlargement of the spleen and lymph nodes may have been partly due to vascular engorgement rather than cellular proliferation alone. The equally sudden return of these organs to relatively normal size is hard to explain on other grounds.

The preliminary diagnosis of infectious mononucleosis could not be maintained, particularly as the Paul-Bunnell tests were performed with non-absorbed sera.

The rapid fall of the haemoglobin level following transfusions (see Fig. 1) suggested that the anaemia was due not solely to replacement of the bone marrow and this was confirmed pathologically by the discovery of widespread erythrophagocytosis and haemorrhage.

## Summary

A girl of 4½ years presented with enlargement of the cervical lymph nodes and spleen, followed by anaemia, leucopenia, fever and enlargement of the liver. Jaundice, thrombocytopenia and a bleeding tendency appeared terminally.

A lymph node removed during life showed appearances typical of Hodgkin's disease but at death the reticulo-endothelial system was replaced by a proliferation of phagocytic histiocytes and giant cells.

I am grateful to Dr. Malcolm Cockburn for the use of the case record and to the Board of the Adelaide Children's Hospital for permission to publish the material. Thanks are due to Mr. Ray Boyd for the preparation of the illustrations.

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# DEFICIENCY OF VITAMIN $B_{12}$ AFTER EXTENSIVE RESECTION OF THE DISTAL SMALL INTESTINE IN AN INFANT

BY

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Man may survive resection of surprisingly large amounts of the small intestine. As little as 7 in. of jejunum and ileum may be sufficient to support life, at least for a time (Jackson, Linder and Berman, 1951), and a large number of patients have survived less extensive resections and have remained well (Flint, 1912; Haymond, 1935; West, Montague and Judy, 1938; Althausen, Uyeyama and Simpson, 1949). These observations have been made in adults and the results of extensive resections in children during the growing period are less certain. Such operations are infrequently carried out and there is a high immediate postoperative mortality (Benson and Sharpe, 1950). Children may, however, survive resection of large amounts of the small intestine (Blayney, 1901; Flint, 1912), and two infants have recently been recorded whose growth and development were normal after resection of all but 26 to 28 cm. of jejunum and ileum (Pilling and Cresson, 1957).

The purpose of this paper is to describe a child who had an extensive resection of the distal small intestine soon after birth. She later developed a mild megaloblastic anaemia associated with severe $B_{12}$ deficiency and required treatment with vitamin $B_{12}$. Her growth and development have been otherwise normal up to the age of 2½ years.

## Materials and Methods

Haematological methods were those described by Dacie (1956); serum vitamin $B_{12}$ levels were measured by microbiological assay using the *Z* strain of *Euglena gracilis*, according to the method described by Hutner, Bach and Ross (1956); glucose tolerance tests were carried out as described by King and Wootton (1956).

Fat balances were carried out over a continuous nine-day period. The child was given a diet containing approximately 30 g. of fat daily. After a preliminary period of three days, the stools were collected over successive three-day periods and the fat content was estimated by the method of Van de Kamer, Huinink and Weyers (1949).

Absorption of radioactive vitamin $B_{12}$ was measured by the modified faecal excretion technique described by Booth and Mollin (1956). The test dose of vitamin $B_{12}$ was 1 μg. and was given with 50 mg. of a potent intrinsic factor concentrate.

## Case Report

V.R., a female infant, was born at term on March 31, 1957, after a normal pregnancy (birth weight 7 lb. 5 oz.). Soon afterwards she developed signs of intestinal obstruction and was admitted to West Herts Hospital under the care of Dr. M. E. Edmunds. Laparotomy was performed on the 20th day of life and revealed congenital malrotation of the gut with volvulus and extensive gangrene of the small intestine. Approximately four-fifths of the distal small intestine were thought to have been removed, end-to-side anastomosis being performed between the jejunal stump and the mid-transverse colon. The terminal ileum was closed just proximal to the ileo-caecal valve. After an initial period of severe vomiting and diarrhoea, she recovered from the operation, breast feeding was established and she gained weight.

At the age of 3 months she attended The Hospital for Sick Children, Great Ormond Street. At this time she was passing two to five bulky fluid stools daily. She weighed 9 lb. 4 oz., and apart from some abdominal distension, no abnormality was found on examination. She continued with breast feeding and supplements of vitamins A, C and D by mouth. By the age of 6 months her weight (15 lb.) was above the 10th percentile level. Although she continued to have diarrhoea, her weight increased at a normal rate until she was 10 months old, when she weighed 19 lb. (Fig. 1). During the 11th month, however, there was a gradual diminution in the frequency of her stools; she began to vomit after her feeds and she lost weight. She was then admitted to The Hospital for Sick Children at the age of 11 months under the care of Dr. P. R. Evans.

**Clinical Examination.** This revealed a thin child (weight 16 lb. 10 oz.) with generalized abdominal

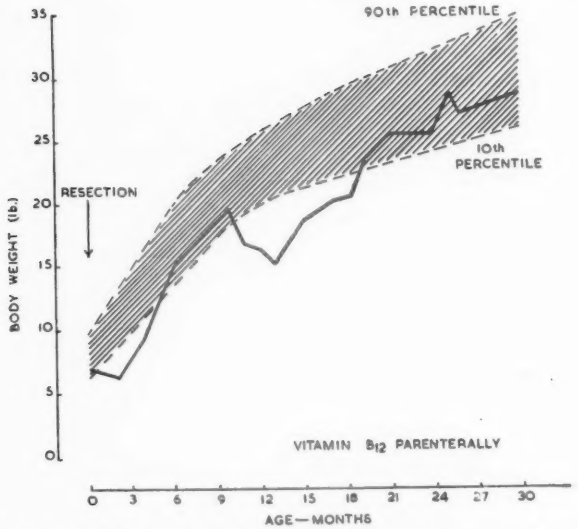


FIG. 1.—Weight chart of patient V.R. after extensive resection of the distal small intestine. Vitamin $B_{12}$ was given parenterally after the thirteenth month. The lines representing the 10th and 90th percentile are also shown (Tanner, 1958).

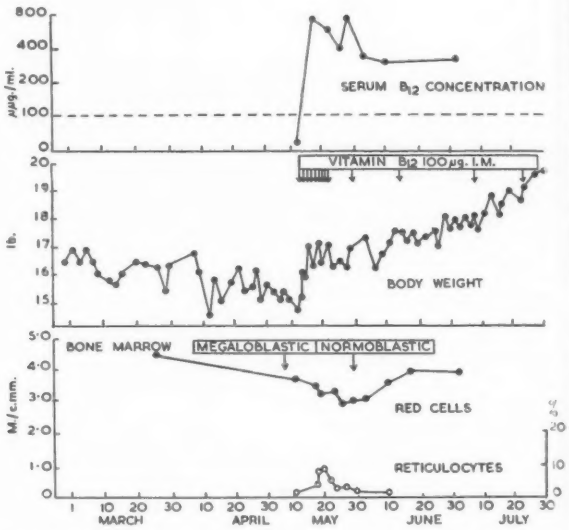


FIG. 2.—Serum $B_{12}$ concentration, body weight, red cells and reticulocytes before and after treatment with vitamin $B_{12}$.

distension. No peristalsis was visible. There was no glossitis nor angular stomatitis. The skin was normal and the central nervous system showed no abnormalities.

**Investigations.** These revealed Hb 12·1 g. % and R.B.C. 4·0 M. per c.mm.; serum electrolytes: Na 140, K 4·2, Cl 102 and $HCO_3$ 26 mEq./litre. Stool cultures were repeatedly negative for pathogenic organisms. Plain radiographs of abdomen showed gross gaseous distension with fluid levels in both colon and small intestine.

**Treatment and Progress.** She was first given oral neomycin (20 mg./lb. body weight in divided doses), but without improvement in her condition. The vomiting, periods of constipation and the radiological evidence of fluid levels in the bowel suggested a diagnosis of subacute intestinal obstruction. A further laparotomy was therefore performed on March 19, 1958, but although the whole of the large bowel and the jejunum immediately proximal to the anastomosis appeared dilated, no organic obstruction was found. The remaining small intestine consisted of the duodenum and approximately 30 in. of jejunum, the end of the jejunum being anastomosed to the middle of the transverse colon, thereby short circuiting the caecum, ascending colon and proximal half of the transverse colon. Nothing further was done and the abdomen was closed.

Her condition continued to deteriorate after this operation. Her weight fell steadily (Fig. 1), vomiting continued intermittently and her stools were bulky and irregular. However, barium meal showed the small intestine to be normal, the barium passing into the colon in one and a half hours. A barium enema outlined the dilated colon but some of the barium remained for five days in the short-circuited ascending colon and caecum, indicating stasis in this loop.

By May 1958, at the age of 13 months, her weight had fallen to 15 lb. (Figs. 1 and 2). Haematological investigations now revealed a mild macrocytic anaemia (Hb 11·0 g. %; R.B.C. 3·7 M. per c.mm.) and the bone marrow was megaloblastic. Her serum $B_{12}$ concentration was 25 µµg. per ml. (normal range 140 to 900 µµg. per ml.). Intestinal function tests were carried out at this time and are shown in Fig. 3. Her absorption of glucose was normal but she had steatorrhoea (mean fat absorption 82% on diet of 30 g. per day) and she was unable to absorb any of the test dose of vitamin $B_{12}$ (Fig. 3).

**Response to Vitamin $B_{12}$.** She was treated with intramuscular injections of vitamin $B_{12}$ (100 µg. daily for nine days, then 100 µg. every two weeks). Her initial response to this treatment is shown in Fig. 2. Vomiting ceased within 24 hours of the first injection and her weight began to increase. Her reticulocytes rose to 9% on the sixth day and the marrow became normoblastic. Although her red cell count fell at first, possibly as a result of rehydration, it then rose to normal levels without other treatment (Fig. 2).

Further investigations revealed no evidence of other deficiencies. Her total serum proteins were 7·0 g. %, serum Ca 8·8 mg. %, inorganic phosphate 5·6 mg. %, and alkaline phosphatase 24 King-Armstrong units. Skeletal radiographs revealed no evidence of rickets. Prothrombin time was normal. Intestinal function studies were repeated after oral chlortetracycline (20 mg./lb. in divided doses for six days). There was no improvement in absorption of either fat or $B_{12}$ following this treatment (Fig. 3).

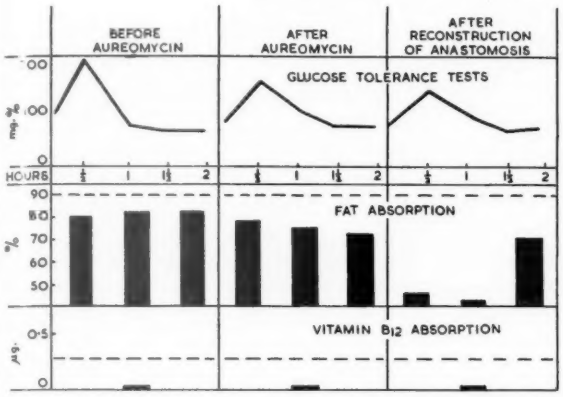


FIG. 3.—Intestinal function tests before and after chlortetracycline (aureomycin) and after refashioning of the jejuno-colic anastomosis. The figures for fat absorption represent the mean absorption per day over successive three-day periods. Normal fat absorption should be greater than 90%. The lower limit of the absorption of radioactive $B_{12}$ by control subjects is indicated by the interrupted line.

Her weight increased steadily, although her stools were unchanged, and she weighed 19 lb. after two months' treatment with vitamin $B_{12}$ (Fig. 2). A further laparotomy was performed on July 30, 1958 (Mr. G. H. Macnab). The jejuno-transverse anastomosis was undone, and an end-to-end anastomosis was made to the caecum. During this procedure many adhesions around the jejunum were broken down. The jejunum appeared slightly hypertrophied immediately proximal to the anastomosis, but the remaining small bowel was of normal calibre. A biopsy taken from the lower end of the jejunum showed normal mucosa, but some hypertrophy of the muscle coats.

She recovered well from this procedure and continued to improve, although a fat balance revealed more marked steatorrhoea than before the operation (mean fat absorption 52% on diet of 30 g. per day). Her glucose absorption remained normal, but she was still unable to absorb vitamin $B_{12}$ (Fig. 3).

After this operation she received a diet usual for her age with restriction of fat to 30 g. per day, together with oral supplements of vitamins A (7,000 units daily), B (Becosym 1 dram daily) and D (1,000 units daily). She was also given vitamin $B_{12}$ intramuscularly (100 $\mu$g. every two weeks). Her subsequent progress is shown in Fig. 1. By 20 months her weight was above the 10th percentile and her development has continued normally. Now, at the age of 2½ years, she weighs 28·5 lb., a normal weight for her age. Her Hb is 10·9 g. % and she remains well, although she still passes three bulky stools daily.

## Discussion

Estimations of the amount of small intestine remaining after resection are notoriously inaccurate (Flint, 1912). At our patient's first operation, it was considered that four-fifths of the small intestine had been removed. The remaining intestine was measured at a later laparotomy and was found to consist of approximately 30 in. of jejunum. The exact length of the small intestine in an infant is not certain and the proportion of the bowel remaining in this patient is therefore not known, but in this case 30 in. may possibly represent between a quarter and a third of the total small intestine.

The type of malabsorption from which she suffered was characteristic of an extensive resection of the distal small intestine (Booth, 1958). Since some of her proximal intestine remained, she absorbed glucose normally, for glucose is rapidly absorbed from the upper small intestine (Verzár and MacDougall, 1936). Her remaining intestine was apparently only sufficient to absorb between 52 and 82% of her dietary fat and she therefore had steatorrhoea, suggesting that fat is normally absorbed more distally than glucose in the small intestine. Her inability to absorb vitamin $B_{12}$ is in keeping with the resection of the distal small intestine, for $B_{12}$ is absorbed in the ileum in man (Booth and Mollin, 1959).

Stagnant loops of bowel may sometimes play a part in causing malabsorption (Cameron, Watson and Witts, 1949; McIntyre, Sachs, Krevans and Conley, 1956; Halsted, Lewis and Gasster, 1956), but do not appear to have been a factor in this case. In patients with such loops, malabsorption is frequently improved by a course of oral broad spectrum antibiotics (Mollin and Baker, 1955; McIntyre *et al.*, 1956; Halsted *et al.*, 1956; Booth and Mollin, 1957) or by operations which remove or correct the loop (McIntyre *et al.*, 1956). Our patient's absorption defects were not improved by antibiotics, nor by the removal of the short circuit at her last operation, and it seems unlikely that the short-circuited area of colon contributed to her malabsorption. The reason for her deterioration in fat absorption after this operation is uncertain, but it may be that the breaking down of adhesions around the lower jejunum resulted in more rapid passage of food through the remaining small intestine.

For the first 10 months of life her growth was normal, suggesting that she was able to absorb or derive from tissue stores sufficient nutrients to maintain normal development during this time. Since she was unable to absorb vitamin $B_{12}$, it is not surprising that she ultimately developed $B_{12}$ deficiency. The delay in onset of this deficiency was presumably due to the time required to exhaust the stores of vitamin $B_{12}$ in liver and other tissues, a situation which is analogous to the delayed development of $B_{12}$ deficiency after total gastrectomy (Pitney and Beard, 1955). The symptoms and

signs in our patient were different from those usually found in adult patients with Addisonian pernicious anaemia. She had vomiting, constipation and signs suggestive of intestinal obstruction, and she lost weight steadily. There were no neurological signs suggesting subacute combined degeneration of the cord or peripheral neuritis. Despite her very low serum $B_{12}$ level, she was not markedly anaemic, her red cells never falling below 3·0 M. per c.mm., although her sternal marrow was megaloblastic.

Her full and complete response to parenteral injections of vitamin $B_{12}$ suggests that although she had marked steatorrhoea, the only deficiency state she had developed was $B_{12}$ deficiency. This observation is supported by the absence of hypoproteinaemia, her normal prothrombin time and the lack of evidence of rickets. Since she has continued to grow normally whilst receiving only vitamin $B_{12}$ parenterally, she appears to be absorbing the other nutrient factors required for growth and development. These factors, including the vitamins other than $B_{12}$, must therefore be absorbed in the proximal small intestine or colon.

It is not certain whether there is any compensatory improvement in intestinal function in children after extensive resections, although adults may show a progressive increase in absorptive capacity following such operations (Althausen, Doig, Uyeyama and Weiden, 1950). It is said that the mucosa and muscle of the remaining gut typically hypertrophies (Flint, 1912; Jackson, 1958), but this does not always occur (Shonyo and Jackson, 1950; Shelton and Blaine, 1954) and in animals the site of the resection may play a part in determining whether there is hypertrophy of the remaining small bowel (Booth, Evans, Menzies and Street, 1959). In our patient, the barium follow-through showed no evidence of hypertrophy of the small intestine, but at laparotomy the lower jejunum was found to be hypertrophied. It is uncertain whether this was due to partial obstruction by the many adhesions found in this area at her last operation, or whether there has been hypertrophy which was compensatory to the loss of intestinal length. It seems unlikely that she will recover the ability to absorb vitamin $B_{12}$ and treatment with vitamin $B_{12}$ by injection is to be continued indefinitely.

The observations in this patient illustrate the importance of the distal intestine in the absorption of vitamin $B_{12}$. They also support the conclusion that patients who have undergone resection of the ileum should either be kept under close haematological supervision or be treated with prophylactic injections of vitamin $B_{12}$.


## Summary

Extensive resection of the distal small intestine was performed in a child soon after birth. Her growth was normal until she was 10 months old when she began to vomit and lose weight. At the age of 13 months she was found to have a mild megaloblastic anaemia and her serum $B_{12}$ concentration was very low. She improved dramatically after treatment with parenteral $B_{12}$ and her growth and development have been normal to the age of $2\frac{1}{2}$ years.


We wish to thank Dr. P. R. Evans and Mr. G. H. Macnab for permission to record details of this patient who was under their care in The Hospital for Sick Children, Great Ormond Street; we are also indebted to Dr. D. L. Mollin for his encouragement and advice, and for permission to quote the results of vitamin $B_{12}$ studies carried out in his laboratory at the Postgraduate Medical School.

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# CHRONIC NON-HAEMOLYTIC JAUNDICE WITH CONJUGATED BILIRUBIN IN THE SERUM AND NORMAL LIVER HISTOLOGY: A CASE STUDY

BY

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Recently our knowledge of bilirubin metabolism has increased considerably. Perhaps the most stimulating discovery has been that bilirubin is excreted in the bile as a glucuronide (Billing, Cole and Lathe, 1957; Schmid, 1957). This has made it possible to classify some rare types of chronic jaundice more definitely. One of these, chronic non-haemolytic familial jaundice, was described many years ago by Gilbert and Lereboullet (1901). Arias and London (1957) concluded from *in vitro* experiments with liver tissue that the cause of this disease was a defect in glucuronide formation. The inability to form glucuronides is also present in the much more severe type of inherited chronic jaundice with kernikterus described by Crigler and Najjar (1952) (cf. Axelrod, Schmid and Hammaker, 1957).

Neonatal jaundice also belongs to this group, characterized by insufficiency of glucuronyl-transferase in the liver (Dutton, 1959), but, in contrast to the diseases mentioned above, is a passing phenomenon, present only in the newborn period (Vest, 1958; Vest and Streiff, 1959).

There is another group of chronic non-obstructive, non-haemolytic jaundice in which no such defect in glucuronide formation is present. In consequence a substantial percentage of 'direct' reacting bile pigment is found in the serum, and bilirubin spills over into the urine. This group includes the form named chronic idiopathic jaundice (Dubin and Johnson, 1954), which is conspicuous by the presence of a pigment similar to lipofuscin in the liver cells (cf. Dubin, 1958). Clinical symptoms are fluctuating jaundice, episodes of abdominal pain, nausea, vomiting, enlarged liver and dark urine. Bromsulphalein retention is greatly increased.

A few reports have appeared on a syndrome similar to the Dubin-Johnson syndrome, where the characteristic pigment was missing on examination of the liver tissue (Rotor, Manahan and Florentin, 1948; Schiff, Billing and Oikawa, 1959; Haverback and Wirtschafter, 1960). There are some other small differences in symptomatology from the Dubin-Johnson syndrome. Most important of these are the absence of attacks of abdominal pain and the fact that the gall bladder can be easily seen on oral cholecystography. Only six patients with this syndrome have been described in the literature so far, to our knowledge. This makes it difficult to decide if the observed differences are constant features of this disturbance of bile pigment metabolism or if they are a variation of the pigmented type of chronic idiopathic jaundice.

The patient described here seems to belong to the non-pigmented group and is presented in the hope of further clarifying the picture of this pigmentless type of chronic non-haemolytic jaundice without insufficiency of glucuronide formation.

## Case Report

W.M., a 7-year-old girl, born in 1952, is the only child of a family from southern Switzerland. The family history gives no indication of liver or blood disease; the pregnancy was normal and the child's birth weight was 3,270 g. At the age of 4 weeks the mother observed a yellow tinge in the skin and this slightly icteric appearance has persisted. It is visible especially in the sclerae, but at times it increases in strength to an overt jaundice. When this happens the child is tired and anorrhexic, but there is no abdominal pain. Sometimes during these attacks the stools are paler than normal and the urine is dark. After a few days these symptoms subside. At the age of 13 months and 16 months the girl was seen by a paediatrician who found no abnormalities apart from icteric sclerae. Liver and spleen were not enlarged, Hb was 67% and 76% respectively. At the age of 28 months the patient was admitted to our hospital because of persistent jaundice.

**First Admission.** On admission skin and sclerae were icteric. The liver was palpable one finger-breadth below the costal margin; the spleen was not enlarged.

Haematological studies showed no abnormalities with the exception of a slightly higher proportion of smaller cells than normal in the Price-Jones curve. Several times the fragility to hypotonic saline solutions was a little increased, total haemolysis occurring at from 0·49 to 0·51%. These features were not persistent, however, and on other occasions normal values were observed. The direct Coombs test and indirect antiglobulin tests for antibodies were negative. Serum bilirubin level was high and varied between 7·2 and 4·2 mg. % with a moderate to strong direct van den Bergh reaction. Urobilinogen level in the urine was also high, but surprisingly no bilirubin could be detected in the urine with the method used at that time.

Extra-hepatic obstruction was thought unlikely from the benign course and from the normal aspect of the faeces. Also, on duodenal aspiration, normal enzyme activity (trypsin, diastase and lipase) was present in the duodenal secretion and A, B and C bile of normal appearance and in normal amounts could be aspirated. Other laboratory findings are shown in Table 1.

Because of the slightly increased red cell fragility and spherocytosis a mild form of hereditary spherocytic anaemia was assumed at that time, despite the rather high bilirubin concentration in the serum and the fact that no abnormalities were found in the parents.

**Second Admission.** In 1959, at the age of 7½ years, the patient was readmitted for further studies because of her persistent slight jaundice with occasional exacerbation. On admission the height was 120 cm. and body weight 23·7 kg. There was a reddening of the throat and a throat culture produced haemolytic streptococci. The antistreptolysin titre was 1:320. Otherwise physical examination was negative, except for the icteric sclerae. Liver and spleen could be felt at the costal margin.

TABLE 1
LABORATORY FINDINGS

| Investigations | 1955 | 1959 |
|---|---|---|
| Haemoglobin | 87% | 90% |
| Red cells millions/mm.³ | 4·36 | 4·26 |
| Colour index | 1·0 | 1·07 |
| Anisocytosis | slight | slight |
| Leucocytes per mm.³ | 7,300 | 9,150 |
| Neutrophils stab | 7·5 | 15·5 |
| Neutrophils segmented | 22·5 | 55 |
| Neutrophils eosinophil | — | 0·5 |
| Neutrophils basophil | — | — |
| Monocytes | 12·0 | 5·0 |
| Lymphocytes | 58 | 23·5 |
| Plasma cells | — | 0·5 |
| Reticulocytes % | 3·5 | 1·3 |
| Platelets | 286,000 | 81,000–160,000 |
| Haematocrit % | 43 | — |
| Ratio of red cells to white cells in bone marrow | 26/100 | 12/100 |
| Price-Jones curve | slight shift to left | normal |
| Osmotic fragility: | | |
| beginning of haemolysis | 0·45 to 0·53% | 0·49% |
| total haemolysis | 0·39 to 0·41% | 0·35% |
| Direct Coombs test | negative | negative |
| Indirect antiglobulin test | negative | |
| Anti-antibodies | negative | |
| Wassermann reaction | negative | |
| Prothrombin | 80–100% | 40–100% |
| Coagulation time | 5 min. | 3 min. |
| Bleeding time (sec.) | 45 | 90 |

TABLE 2
LIVER FUNCTION TESTS

| Investigations | 1955 | 1960 |
|---|---|---|
| Serum bilirubin (mg. %) | 4·2–7·2 | 3·7–5·0 |
| Direct | + | 2·2–3·5 |
| Cholesterol (mg. %) | | 177 |
| Esters | | 72% |
| Total protein (g. %) | | 5·3–6·7 |
| Serum iron (μg. %) | 54–86 | 116 |
| Blood sugar (mg. %) | 93 | |
| Serum alkaline phosphatase | | 12 |
| Takata-Ara | (+) | + |
| Cadmium reaction | | trace |
| Thymol turbidity, units | | 2·3 |
| Transaminase: | | |
| SGOT, units | | 29 |
| SGPT, units | | 12 |
| Galactose tolerance | normal | normal |
| 'Bromsulphalein' retention | — | 51% and 48% |
| Hippuric acid test | — | low normal |
| NAPA-test for glucuronide formation | — | normal |
| Urine: | | |
| Urobilinogen | increased | 4·9 mg./24 hrs |
| Bilirubin | | 0·62 mg./24 hrs |
| Coproporphyrin | | trace |
| Melanin | | negative |
| Duodenal fluid: | | |
| Trypsin | normal | normal |
| Diastase | normal | normal |
| Lipase | normal | normal |

BLOOD FINDINGS. The red cell count was 4·26 million, Hb 89% and colour index 1·07. Some anisocytosis was discernible. Reticulocytes 1·3%; white cell count 9,150 per c.mm. The differential count and additional haematological data are listed in Table 1.

LIVER FUNCTION (Table 2). Takata-Ara reaction was one plus; cadmium, a trace; thymol-turbidity 2·3 units; total serum protein 5·35 and 6·7 g. %. Paper electrophoresis revealed albumin 48%, $\alpha_1$-globulin 5·8%, $\alpha_2$ 11·6%, $\beta$ 13·4%, and $\gamma$-globulin 21·2%. The increase in $\gamma$-globulin was probably produced by the existing throat infection. Serum transaminase glutamic oxalacetic, 29 units; glutamic pyruvic, 12 units; serum alkaline phosphatase, 12 units; cholesterol, 177 mg. %; cholesterol esters, 72%. The prothrombin activity was 40% on admission, but afterwards, on repeated determinations, was always normal.

Serum bilirubin determination (methods of Jendrassik and Gróf, 1938; Malloy and Evelyn, 1937) gave values between 5·0 and 4·1 mg. % for total bilirubin, the direct reacting pigment being 3·5 to 2·2 mg. %. Paper chromatography of the serum by the method of Schmid (1957) showed two bands of azoderivatives with an Rf of 0·46 and 0·58.

URINE. Urines generally were rather dark in colour. Urobilinogen excretion (average of two 24-hour collections) amounted to 4·86 mg. per day and therefore was greatly increased (method of Schwartz, Sborov and Watson, 1944). As expected from the increased amount of 'direct' reacting bile pigment in the serum, some bilirubin was excreted in the urine (0·62 mg. per 24 hours) (method of With, 1942). Only a trace of porphyrin was found and a qualitative test for melanin was negative. Amino-nitrogen excretion was normal (31 mg. per 24 hours) and the amino-N-coefficient was 1·7.

STOOLS. The stools were of normal colour. The faecal urobilinogen excretion (average of two 24-hour collections) was 32·25 mg. per day, a value that is normal for this age group (method used for estimation, Schwartz *et al.*, 1944). The total bile pigment excretion (stools and urine) in 24 hours amounted to 37·1 mg. The haemolytic index (calculating a blood volume of 1,900 ml.) was 15. This normal value excluded an accelerated red cell destruction. The ratio of faecal to urinary urobilinogen was very low, 6·6:1 (the normal is about 100:1), showing that a much larger amount of urobilinogen was excreted by the kidneys than is normal.

'BROMSULPHALEIN' TEST. After intravenous injection of a dose of 5 mg. of 'bromsulphalein' (BSP) per kg. body weight, the retention in the blood 30 minutes later was 51%. On repetition of the test five weeks later, it was 48% (normal at this age 0-1·5%). The dye was detectable in the duodenal aspirate 45 minutes after the injection, whereas it normally appears within the first 15 minutes. The peak concentration of 66 mg. % in the duodenal fluid was reached after 70 minutes and two hours after the injection the concentration was still higher than 50 mg. %. Because of the difficulties in recording duodenal fluid volume it is not possible to give figures for absolute amounts excreted. In the urine 14·6% of the injected dose of BSP (125 mg.) was excreted in the first two hours after administration; the following portions contained progressively smaller amounts, but even 18 hours later the BSP concentration was still 1·9 mg. %. The results of the test are shown in Fig. 1. In addition chromatography of BSP metabolites in the serum 15, 30, 120 and 420 minutes after injection by the method of Carbone, Grodsky and Hjelte (1959) gave values of 5·3%, 5·4%, 17% and 26% respectively for BSP conjugates. This indicates an increase in the percentage of conjugated BSP concurring with a decrease in free BSP. In the bile, apart from free BSP, up to three BSP-conjugated were present, with Rf-values of 0·64, 0·57 and 0·40. From these findings an impairment of 'bromsulphalein' excretion is evident which seems to be caused not so much by a deficiency of conjugation as of secretion.

HIPPURIC ACID TEST. After intravenous injection of 1·5 g. benzoic acid the patient excreted 0·59 g. hippuric acid in the urine within the following one-hour period. In our experience this can be considered as a low normal result in a child of this age. Glycine conjugating ability seems not to be impaired to a great extent.

GLUCURONIDE FORMATION. N-acetyl-p-aminophenol (NAPA) was used as a substance to test the ability of the patient to form glucuronides. After oral or intravenous administration this substance is conjugated at the hydroxyl-group and excreted as glucuronide and sulphate in the urine. In adults the recovery within 24 hours is about 70 to 80% of the dose administered. Estimation of free NAPA in the serum and urine (Brodie and Axelrod, 1948) before and after hydrolysis with β-glucuronidase makes it possible to calculate the amount of NAPA conjugated with glucuronic acid (Vest and Streiff, 1959). Fig. 2 shows the results obtained with this test after intravenous injection of 240 mg. of N-acetyl-p-aminophenol. Retention in the serum was 7·6% after six hours (normal values are less than 10%). The curve showing the concentration of NAPA-glucuronide at various time intervals also takes a normal course. The girl excreted in the urine 72·7% of the dose injected within 24 hours. Of this 10·8% was in the free form, 45% conjugated with glucuronic acid and the rest with sulphate. Fig. 2 also shows the increase of glucuronic acid in the serum, which occurred after administration of NAPA. On the other hand this load did not influence the level of the serum bilirubin. The excretion of glucuronic acid (estimated by the method of Dische, 1947) in the urine amounted to 57 mg. per 12 hours during a control period. After the injection of the NAPA it rose to 177 mg. in the first 12-hour period and to 107 mg. in the second. These findings show that glucuronide formation is not deficient in this patient.

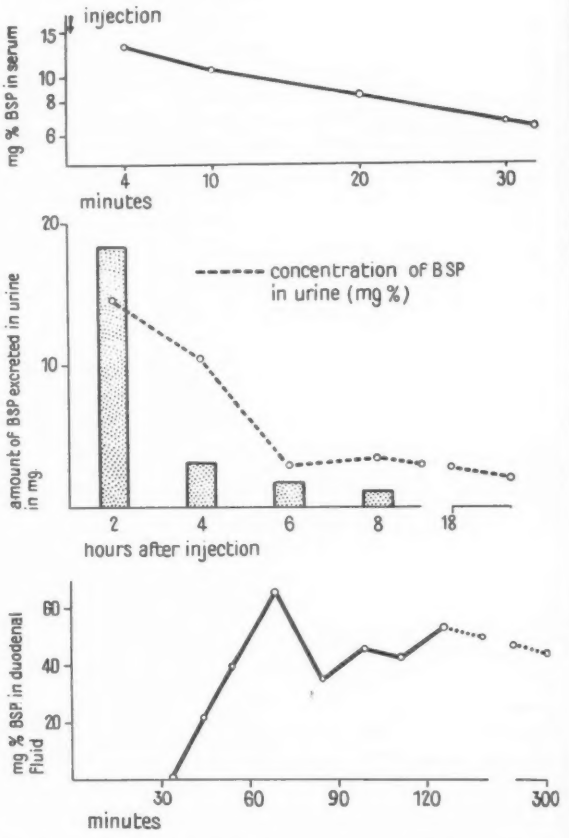


FIG. 1.—Bromsulphalein test; Upper part, concentration of 'bromsulphalein' in the serum after injection of BSP 5 mg. per kg. body weight, retention after 30 minutes, 51%; Middle part, amount of BSP excreted in the urine in four two-hour periods and concentration of BSP in the urine at various intervals after injection; Lower part, time of appearance and concentration of BSP in the duodenal fluid.

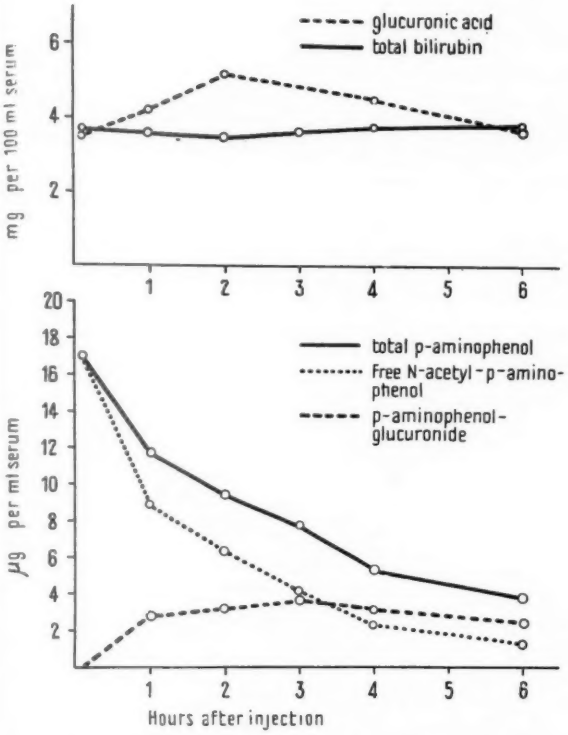


FIG. 2.—Test for the ability of the liver to form glucuronides; Upper part, concentration of glucuronic acid and total bilirubin in the serum at various times after injection of N-acetyl-p-aminophenol in a dose of 10 mg. per kg. body weight; Lower part, concentration of total p-aminophenol, free N-acetyl-p-aminophenol and p-aminophenol-glucuronide in the serum after the NAPA load.

RADIOGRAPHIC EXAMINATION. An oral cholecystography with four tablets of iopanoic acid (Cistobil 'Cilag') showed a well-filled gall bladder shadow. After ingestion of egg-yolk a contraction of the vesicle was clearly visible.

LIVER BIOPSY. A liver biopsy was performed, using a Menghini needle (Menghini, 1958). Histological examination* revealed normal liver tissue with an unaltered lobular hepatic structure. There was no increase in connective tissue in the portal tracts. The small bile ductules were not dilated and there were no bile thrombi in the bile capillaries. Glycogen was present in the liver cells in normal amounts. No abnormal pigmentation was seen either in the liver or in the Kupffer cells.

## Discussion

This patient presented the following symptoms: a chronic jaundice with a serum bilirubin level between 4 and 7 mg. %, 50 to 70% of which reacted directly in the van den Bergh reaction; a normal urobilinogen excretion in the stools but an increased amount of urinary urobilinogen and bilirubinuria; a markedly impaired BSP test, apparently without gross deficiency of conjugation; a low normal hippuric acid test; a normal glucuronide formation in a N-acetyl-p-aminophenol loading test; no evident signs of hepatocellular damage (normal flocculation-tests, normal prothrombin, normal transaminase, etc.), and a liver biopsy showing no alterations.

The absence of anaemia and increased erythropoiesis, the normal amounts of urobilinogen in the stools and the considerable concentration of 'direct' bilirubin in the serum indicate that the icterus is not haemolytic in origin.

An incomplete biliary obstruction should lead to reduced faecal bile pigment. In addition, some signs of liver damage would be expected after an obstruction of this duration, but were not present in this patient. The results of the liver biopsy and the prompt filling of the gall bladder on cholecystography also rule out a biliary obstruction.

Constitutional hepatic dysfunction (Gilbert's disease) can be excluded on the basis of normal glucuronide formation, the occurrence of direct bilirubin in the serum, the bilirubinuria and the abnormal BSP retention.

The case can be differentiated from chronic idiopathic jaundice (Dubin-Johnson; black liver jaundice) by the absence of the characteristic pigment in the liver cells and the filling of the gall bladder on oral cholecystography. The symptom of abdominal pain, so commonly found in the Dubin-Johnson disease, was also missing. It seems likely therefore that this girl belongs to the group of patients with non-haemolytic jaundice with conjugated bilirubin in the serum, first described by Rotor *et al.* (1948), where no pigmentation is present in the liver cells.

In contrast to the observations of Schiff *et al.* (1959) urinary urobilinogen excretion was increased in this patient. This corroborates Haverback and Wirtschafter (1960) who found high urinary urobilinogen levels in their two patients. Increased values of urinary bile pigment have also been found in chronic idiopathic jaundice with liver cell pigmentation (Dubin, 1958).

There is also some discrepancy with the findings of Schiff *et al.* (1959) with regard to the percentage of 'bromsulphalein' conjugates in the serum after BSP injection. They report 6% and 4% respectively at 45 and 90 minutes and we found 5·3% at 15 minutes, 5·4% at 30, 17% at 120 and 26% at 420 minutes. From this it would seem that the percentage of conjugates increases with time.

*Professor F. Roulet performed the examination of the liver biopsy specimen.

Perhaps, as with bilirubin, there is no deficiency of 'bromsulphalein' conjugation but mainly of secretion and this leads to the diminished removal rate from the plasma.

Nothing is known about the nature of the defect in this syndrome. Because an insufficiency of bilirubin glucuronide formation has been ruled out by all investigators, an impairment in the hepatic excretion of bilirubin glucuronide and a diminished uptake of bilirubin by the hepatic cells has been postulated (Schiff *et al.*, 1959). The familial occurrence makes it possible that the defect is a genetic error of metabolism. Males and females can be affected. The condition seems to be compatible with normal life as evidenced by the stationary state of health of Rotor's original patients (Rotor, 1960) more than 12 years after their initial examination.

## Summary

A case of non-haemolytic, chronic jaundice in a girl, 7 years of age, is presented. The pertinent findings were onset of jaundice at 4 weeks of age, serum bilirubin levels between 4 and 7 mg. %, 50 to 70% of which gave a direct reaction, normal urobilinogen excretion in the stools, but increased urinary urobilinogen and bilirubinuria, 'bromsulphalein' retention of 50% after 30 minutes and low normal hippuric acid formation. The ability to conjugate with glucuronic acid in a N-acetyl-p-aminophenol loading test was normal. Oral cholecystography revealed a normal gall bladder. Other liver function tests were essentially normal. Liver biopsy showed a regular structure and appearance of the liver tissue without pigmentation. Chronic idiopathic jaundice (Dubin-Johnson syndrome) could therefore be ruled out and the patient was classified as a case of jaundice of the type described by Rotor *et al.* (1948).

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# ARTERIOVENOUS ANEURYSM OF THE GREAT VEIN OF GALEN WITH HEART FAILURE IN THE NEONATAL PERIOD

BY

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The great cerebral vein of Galen extends from the junction of the two internal cerebral veins under the splenium of the corpus callosum to the commencement of the straight sinus. Arteriovenous aneurysms of this vein are rare congenital anomalies and only 22 cases have been found in a review of the literature.

Other types of cerebral arteriovenous aneurysms are not so unusual. Their true incidence has become more apparent following the widespread use of angiography. Mackenzie (1953) estimated their occurrence as 1% of all neurological admissions. By way of contrast Paterson and McKissock (1956) found no example of great cerebral vein aneurysm in 110 cases of cerebral arteriovenous aneurysm, and the same is true of the series reported by Olivecrona and Riives (1948), Mackenzie (1953) and Potter (1955). These vascular malformations are predominantly of two main types (Hamby, 1952). In the first type, there is a direct end-to-end connexion between an artery and vein, and in the second a network of poorly differentiated, non-capillary vessels intervenes between an artery and several veins, forming a mass of abnormal, dilated and tortuous vessels which sometimes goes by the name of 'angioma' but is not generally considered to be neoplastic. In both types veins not directly involved in the malformation may become enlarged and tortuous in response to the raised venous pressure. The great cerebral vein, however, only shows aneurysmal dilatation when there are one or more abnormal arterial vessels opening into it, its immediate tributaries or continuation. Other vascular malformations of the brain may coexist. These abnormal arterial vessels have arisen, in the described cases, from the posterior cerebral, posterior communicating, callosal and superior cerebellar arteries and from the choroid plexus of the third ventricle.

Local and general effects may be exerted on the cardiovascular system as in other varieties of arteriovenous aneurysm. The general effects may be difficult to detect. They include a variable increase in pulse pressure, tachycardia, apical systolic murmur and evidence of some enlargement of the heart. The literature contains reports of two babies who died of heart failure associated with a cerebral arteriovenous aneurysm not involving the great cerebral vein (Silverman, Breckx, Craig and Nadas, 1955) (Table 2) and three cases associated with an arteriovenous aneurysm of that vein (Table 1, Cases 11, 13 and 14). One of these infants had coarctation of the aorta as well.

The two cases reported here also died of heart failure associated with arteriovenous aneurysm of the great vein of Galen.

### Case Reports

**Case 1.** S.F. was born September 15, 1959, by normal delivery at about 38 weeks' gestation. The birth weight was 2,240 g. and the head circumference was 33 cm. Respiration was established immediately.

Lower rib recession was noted 16 hours after birth and became more severe. The baby's extremities became cyanosed, peripheral pulsations were poor, there was a soft systolic murmur and the liver became enlarged. The respiratory rate rose to 70 per minute. This picture of respiratory distress and early heart failure was complicated by the occurrence of head retraction and opisthotonus 30 hours after birth followed by twitching and frank fits. Fontanelle tension was normal. Blood calcium was normal. Blood glucose levels were persistently low, 23 and 15 mg. % in the first 24 hours and never above 15 mg. % subsequently in spite of hourly glucose feeds. Lumbar puncture showed xanthochromic fluid under moderately increased pressure with 14,700 red and 75 white blood cells per cu. mm.

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24 CASES OF ARTERIOVENOUS ANE

| Author | Case No. | Lesion and Arterial Supply | Presenting Symptoms or Si | t Onse |
|---|---|---|---|---|
| Steinheil (1895) | 1 | Left callosal artery; great and one small cerebral vein dilated; sacculated aneurysm on pedicle on great cerebral vein. Associated right frontal vascular malformation | Convulsions; left hemianop ia | Child |
| Jaeger, Forbes and Dandy (1937) Jaeger and Forbes (1946) | 2 | Huge dilated great cerebral vein pressing on aqueduct; large branches off both post. cerebral arteries into small cerebral veins; further vascular malformations | Internal hydroceph.; epist axis, | mths |
| Russell and Nevin (1940) | 3 | Atresia of int. jugular veins. Left post. cerebral artery branch to great cerebral vein; serpentine mass of vessels | Prominent face and neck veins; motor development; exoph cranial bruit | mths |
| Russell and Nevin (1940) | 4 | Sup. callosal art. and post. cerebral arteries, branches to great cerebral vein; aneurysm compressed aqueduct | Hydrocephalus; distended scalp | mths |
| Alpers and Forster (1945) | 5 | Choroidal artery and post. cerebral arteries, branches to aneurysm of great cerebral vein | Mental retardation CNS signs; hydrocephalus | yrs |
| Oscherwitz and Davidoff (1947) | 6 | Tumour probably represented aneurysm of great vein of Galen and branches of circle of Willis | Headaches | yrs |
| Lumsden (1947) | 7 | Aneurysm on upper surface of tentorium attached to near great vein of Galen at junction of inf. sagitt. sinus and straight sinus; ? small artery from choroid plexus of 3rd ventricle | Fits; intraventric. and subarach. rhage | mths |
| Boldrey and Miller (1949) | 8 | Branches of post. cerebral artery to aneurysm of great cerebral vein; pulsatile mass of vessels behind right mastoid | Hydrocephalus; dilated face, sca pulsatile mass behind mastoid; subarach. haemorrhage | mths |
| Boldrey and Miller (1949) | 9 | Post. communic. and post. cerebral arteries connected to great cerebral vein (angiogram) | Swollen face, eye veins; fatiguabi | Birth |
| Wolfe and France (1949) | 10 | 'At least one artery entered aneurysm of great vein of Galen' | Fits; CNS signs; int. hydroceph | yrs |
| Pollock and Laslett (1953) | 11 | Post. cerebral and sup. cerebral arteries communic. with aneurysm of great vein of Galen and sag. sinus; also vessels from int. cerebral veins, most of supply vessels appeared to be thrombosed | Heart failure; large head | Birth |
| Petit-Dutaillis, Guiot and Berdet (1953) | 12 | Branches of post. cerebral arteries to aneurysm of great vein of Galen | Hydrocephalus | 4 mths |
| Clément, Gerbeaux, Combes-Hamelle, Pertuiset and Petranca (1954) | 13 | Feeding vessels to aneurysm of great cerebral vein not identified; much thrombus | Dyspnoea; increased muscul dysphagia; cyanotic attacks | ? Birth 0 days |
| Clément *et al.* (1954) | 14 | Post. cerebral arteries communicn with aneurysm of great cerebral vein; also 'very abnormal arterial distribution' | Failure to thrive; wasting; hy dilated veins; cranial bruit; | ? 3 wk |
| Clément *et al.* (1954) | 15 | Personal communication on similar case | No details | Infanc |
| French and Peyton (1954) | 16 | Anterior cerebral artery group communic. with great cerebral vein | Large head; failure to thrive retardation | 2 mth |
| French and Peyton (1954) | 17 | Abnormal mass of vessels on medial side. Right cerebral hemisphere, communic. with great cerebral vein, ant. callosal artery enlarged | Sub-arach. haemorrhages | ? |
| French and Peyton (1954) | 18 | Arteriovenous malformation near pineal with rapid filling of great vein of Galen; abnormally large ? left ant. cerebral artery | Headache; slurred speech | ? |
| French and Peyton (1954) | 19 | Branches of post. cerebral arteries into much dilated great vein of Galen | Headaches; subarach. haemorrh | ? |
| French and Peyton (1954) | 20 | Enlarged sup. great cerebral artery into large aneurysmal sac near pineal, draining into dilated great vein of Galen | Headaches; photophobia; lethargy; subarach. haemorrh tal illness | ? |
| Hirano and Terry (1958) | 21 | Branches of post. cerebral arteries seemed to end blindly in wall of aneurysm of great cerebral vein | Hydrocephalus, epistaxis, pro pyrexia, ? cause | 5 mt |
| Gibson, *et al.* (1959) | 22 | Branches of post. cerebral artery to aneurysm of great cerebral vein, compressing aqueduct | Hydrocephalus | 6 mt |
| Claireaux and Newman (Case 1) | 23 | Arteriovenous aneurysm of both post. cerebral arteries and great cerebral vein | Heart failure, fits, opisthotonos | 16 hrs |
| Claireaux and Newman (Case 2) | 24 | Arteriovenous aneurysm of right post. cerebral artery and great cerebral vein | Neck retraction | 24 hrs |

HE GREAT CEREBRAL VEIN OF GALEN

| t Onset | Age at Diagnosis | Associated Cardiovascular Signs | Surgery | Outcome |
|---|---|---|---|---|
| hild | 49 yrs | — | — | Died |
| mths | 4 yrs | Murmur and increased cardiac dullness after 'flu at 8 mths; bruit in neck at 27 mths, low blood pressure, anaemia; carotids dilated, also jugulars | Carotid ligation | Died |
| mths | 17 mths | — | — | Died |
| mths | 17 mths | None in life | Decompression | Died |
| yrs | 18 yrs | — | Craniotomy | Died |
| yrs | 27 yrs | Soft blowing systolic murmur | Craniotomy | Alive |
| mths | 7 mths | — | — | Died |
| mths | 16 mths | — | Carotid ligation; clipping of feeding arteries | Alive |
| Birth | 15 yrs | — | Carotid ligation | Alive |
| yrs | 21 yrs | — | Torkildsen's operation | Died |
| Birth | 4 days | Heart failure | — | Died |
| mths | 4 mths | — | — | Alive |
| Birth<br>days | 1 mth | Heart failure | — | Died |
| 3 wks | 7 mths | Heart enlarged; coarctation of aorta | — | Died |
| nfancy | — | — | — | Died |
| mths | 21 mths | — | Craniotomies; clipping of feeding arteries | Alive |
| ? | 12 yrs | — | Clipping of feeding arteries | Alive |
| ? | 22 yrs | — | Clipping of feeding arteries | Alive |
| ? | 14 yrs | — | — | Alive |
| ? | 43 yrs | — | Craniotomy | Alive |
| mth | 28 mths | — | — | Died |
| mth | 4½ yrs | — | Anastomosis of spinal theca to peritoneum | Died |
| hrs | 4 days | Cyanosis, systolic murmur, neck pulsations, heart failure | — | Died |
| hrs | 16 days | Cyanosis, systolic murmur, neck pulsations | — | Died |

:—Ni or not mentioned

TABLE 2

HEART FAILURE ASSOCIATED WITH CEREBRAL ARTERIOVENOUS ANEURYSM NOT INVOLVING GREAT CEREBRAL VEIN OF GALEN

| Author | Case No. | Lesion and Arterial Supply | Presenting Symptoms or Signs | Age at Onset | Age at Diagnosis | Associated Cardiovascular Signs | Surgery | Outcome |
|---|---|---|---|---|---|---|---|---|
| Silverman *et al.* (1955) | 1 | Right cerebral hemisphere almost replaced by massive vascular network penetrating right frontal bone; right middle and post. cerebral arteries gave branches to communicate with dilated sup. sagitt. sinus | Dyspnoea; cyanosis | 4 hrs | 1 day | Systolic murmur; right carotid thrill; cardiac enlargement and failure | — | Died |
| Silverman *et al.* (1955) | 2 | Large cirsoid aneurysm between middle cerebral artery and sigmoid sinus; large tortuous vascular channels | Respiratory distress; cyanosis; shrill cry | 30 hrs | 3 days | Systolic murmur; venous congestion; cardiac enlargement | — | Died |

The cerebrospinal fluid glucose level was 30 mg. %. The opisthotonus improved markedly after the lumbar puncture but relapsed. The fits, some left sided, recurred. Neck pulsations became very vigorous. Venous congestion, further enlargement of the liver and peripheral oedema developed. Digitalization caused only a transient and partial reversal of these signs. An electrocardiogram showed digitalis effect and increased P waves and some evidence of left as well as of right ventricular enlargement. The baby died on the fourth day, in heart failure. Blood glucose levels had shown no sign of rising.

ELECTROENCEPHALOGRAM. 'The pattern of this record is that of a full term normal baby when awake and sleeping. There is perhaps a little more rhythmic activity at 15 c./sec. than usual but this may be accounted for by the prematurity. This activity is mostly seen when the baby is awake and is up to 25 μV in amplitude. When the baby is asleep there are repeated single or multiphasic sharp waves up to 250 μV in amplitude and up to duration 0·5 sec. These slow sharp waves are unilateral and occur simultaneously over all areas of the head and about equally on both sides' (Dr. Ruth Harris).

RADIOLOGY. Skull radiograph revealed no abnormality; chest radiograph showed only moderate cardiac enlargement.

NECROPSY. The body was that of a small male infant weighing 2,150 g. The dura mater and pia arachnoid were healthy. The brain (333 g.) was firm. The torcular Herophili was greatly enlarged and contained firm clot. Clot was also present in the superior and inferior longitudinal sinuses, the transverse sinuses and the jugular bulbs. The jugular veins appeared to be normal. At the base of the brain a large aneurysm was found. This was largely composed of a grossly distended great cerebral vein of Galen which communicated anteriorly with both posterior cerebral arteries and posteriorly with the distended torcular (Fig. 1). The aneurysmal sac measured 2·2 × 1·5 cm. The arterial communication was complex. The basilar artery divided anteriorly into the right and left posterior cerebral arteries in the usual manner. The right posterior cerebral artery then divided immediately into four and these reunited after passing downwards and backwards for a distance of 3 cm. The thick vessel thus formed then subdivided again before uniting with the aneurysm (Fig. 2). The left posterior cerebral artery divided into three and the branches joined the anterior part of the aneurysm. The great cerebral vein after receiving the internal cerebral veins expanded into a thick-walled sac. This sac received both posterior cerebral arteries and these passed backwards to join the torcular Herophili. The aneurysm had a bulbous anterior portion, a narrow neck and a fusiform body. The cerebral veins were not distended. The lower portion of the

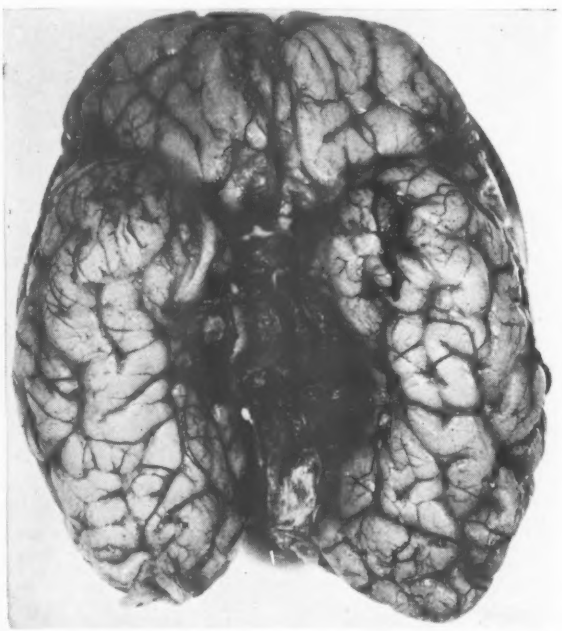

FIG. 1.—Case 1, brain; the inferior surface is exposed to show the aneurysm of the great cerebral vein and the abnormal communications with the posterior cerebral arteries.

aqueduct of Sylvius was of normal calibre and the fourth ventricle was not distended. The anterior surface of the cerebellum was hollowed in the region of the aneurysm. The brain was congested.

The pericardium was clear and glistening and there was a moderate quantity of clear, yellow fluid in the pericardial sac. The heart was enlarged as a result of dilatation of the right atrium and right ventricle. Both chambers contained a large amount of blood clot. The foramen ovale and ductus arteriosus were patent. The valves and great vessels had a normal appearance.

The larynx, trachea and bronchi were healthy. The lungs were congested and some subpleural haemorrhages were present. On slicing a few haemorrhagic areas were noted. The stomach and bowel were healthy. The liver (52 g.) and spleen (5 g.) were not enlarged. The genito-urinary tract was healthy and the endocrine glands showed no abnormality. Supernumerary digits were present on the lateral border of each hand. There was a complete extra finger on the left hand and a rudimentary one on the right. The fifth toe of the right foot was bifid.

HISTOLOGY.

*Lungs.* The pleura was healthy. The lungs were congested but quite well expanded. Some patchy haemorrhage was present. In some areas the alveolar ducts and alveoli were flooded with red cells. The bronchi were healthy. There was no pneumonia.

*Aneurysm.* A section was taken through the most dilated portion of the great cerebral vein. The lumen contained fibrin thrombus. The wall was quite thin and there was evidence of degeneration. No intima was recognized.

*Left Posterior Cerebral Artery.* The lumen was occluded by fresh thrombus which showed no evidence of organization. The vessel was distended as a result of the enclosed thrombus. The wall showed no degenerative change.

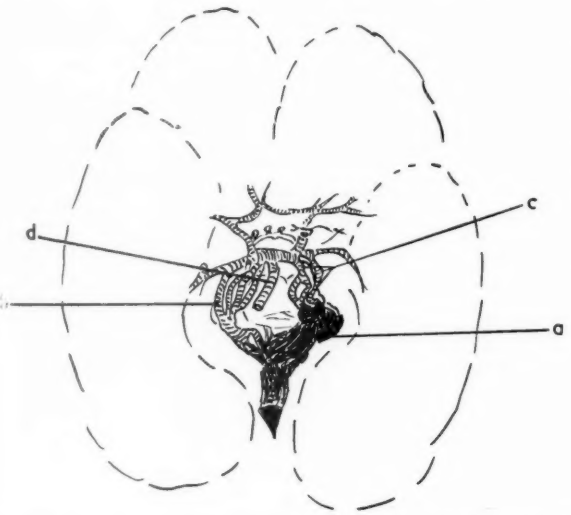


FIG. 2.—Case 1, brain; outline drawing to show (*a*) aneurysm of great cerebral vein, (*b*) right posterior cerebral artery with abnormal branching, (*c*) left posterior cerebral artery, (*d*) basilar artery.

SUMMARY. Cerebral arteriovenous aneurysm; intrapulmonary haemorrhage; supernumerary digits on each hand and bifid right fifth toe.

**Case 2.** The mother, 23 years of age, para 0 had bilateral active tuberculosis and during pregnancy had to be treated for pyelonephritis resulting from infection with *Escherichia coli*. She went into labour at term and the infant was delivered spontaneously. The first stage of labour lasted 18 hours 30 minutes and the second stage 30 minutes. There was a vertex presentation.

The infant was a male and weighed 3,715 g. at birth. The head circumference was 32·5 cm. The infant's condition was good and he cried immediately. There was no peripheral cyanosis but cardiac pulsation was noted to be vigorous and there was strong arterial pulsation in the neck. A systolic murmur was heard over the apex. On radiological examination the heart was seen to be enlarged. One week after birth cyanosis was observed and there was slight pitting oedema of the feet and legs. The pulse rate was 160 per minute and respirations 40 per minute. A diagnosis of congenital malformation of the heart was made. Further radiological examination on the 11th day showed an increase in the size of the heart. Cyanosis became more marked and neck retraction was noted. The infant's condition steadily deteriorated and he died 16 days after delivery.

NECROPSY. The body was that of a well developed male infant and weighed 3,345 g. The sternum was prominent. The falx and tentorium were intact. The brain (400 g.) was very soft and markedly congested. The great cerebral vein was replaced by a large saccular aneurysm 4·5 cm. in length and 2 cm. in diameter. This aneurysm was attached to the junction of the falx with the tentorium. It communicated anteriorly with the right and left internal cerebral veins and with the right posterior cerebral artery. The cerebral veins were engorged but not thrombosed. There was slight dilatation of the lateral ventricles and of the third ventricle which contained clear cerebrospinal fluid. The aqueduct was patent and the fourth ventricle was of normal size. A small amount of subarachnoid haemorrhage was present over the cerebellum. On slicing the aneurysmal dilatation of the great cerebral vein was found to contain organized thrombus.

The pericardium was clear and glistening, there was a small quantity of clear, straw-coloured fluid in the pericardial sac. The heart was considerably enlarged, chiefly as a result of hypertrophy and dilatation of the right atrium and right ventricle. The interventricular septum was intact and very broad. Thick post-mortem clot was present in the right atrium. There was no structural abnormality of the heart valves or of the great vessels. The foramen ovale was closed. The ductus

glycaemia. Clinical features of this type of arteriovenous aneurysm are reviewed and it appears that hydrocephalus and severe cardiovascular effects are commoner than in the 'angioma' type of cerebral arteriovenous aneurysm. Surgery appears to hold out the possibility of cure in some cases, provided that diagnosis and angiography anticipate the potentially rapid decline of such patients.

Our thanks are due to Professor A. Moncrieff and Dr. J. P. M. Tizard for access to the clinical data of Case 1. The photographs were prepared by Mr. E. Clark, the Bernhard Baron Memorial Research Laboratories, Queen Charlotte's Maternity Hospital.

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## Addendum

Since this paper has been sent to the press, two additional cases of cerebral arteriovenous fistula associated with heart failure have been reported by Glatt and Rowe (1960).

# TWO CASES OF RETICULOENDOTHELIOSIS—LETTERER SIWE SYNDROME

BY

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Diseases characterized by proliferative changes in the reticulo-endothelial system, other than the leukaemias and specific infections such as tuberculosis and typhoid fever, give rise to three main syndromes in children, but there are many atypical and intermediate forms. Originally described as three separate conditions, these syndromes, namely Letterer-Siwe disease, Hand-Schüller-Christian syndrome, and 'eosinophilic granuloma' of bone are now believed by many authorities to have a common aetiology, as yet unknown, and basic pathology. Van Creveld (1951) is of the opinion that a distinction between the first two is unnecessary and at times impossible, and clinical pictures occupying intermediate positions between them and even sharing features of the infectious reticuloses have been described; Siwe (1949) on the other hand, maintained that they were pathologically distinct. Those authors who accept the theory of unity of Letterer-Siwe disease and Hand-Schüller-Christian syndrome do so on the assumption that lipoid storage would develop in the former if the disease were protracted; moreover, sequences of the three morbid pictures in one patient on consecutive biopsies have also been described by Bartels (1947), Wentholt and Hadders (1949), Love and Fashena (1948), and Parkinson (1949). That this sequence of events is not always followed has been shown elsewhere and is further demonstrated by the protracted course of one of the cases to be described, but in it account must be taken of the modifying effects of steroids.

Considerable evidence is accumulating on the value of ACTH and cortisone in the treatment of the three syndromes, particularly of the subacute and chronic forms of the Hand-Schüller-Christian syndrome. Karlen (1952) reported disappearance of hepatosplenomegaly and exophthalmos in an 18-month-old girl on cortisone therapy, but relapse occurred when the treatment was stopped on account of severe oedema, and the patient died. Røjel and Lund (1958) described a boy with Hand-Schüller-Christian syndrome aged 14 months at onset, but not diagnosed till 3 years and 9 months, who was pronounced cured after three years' treatment with ACTH and cortisone, but he was observed for only three months after cessation of treatment, and had received x-ray therapy also.

Sewell (1954) presented a girl of 3 years 10 months to the Royal Society of Medicine who had shown histological features of eosinophilic granuloma of bone and later of Hand-Schüller-Christian syndrome with clinical improvement on cortisone after failure to respond to Xrays; and Flosi, Assis, Coelho Neto, Bloise, Ulhôa Cintra and Barros (1959) described a complete remission after four years almost continuous treatment with cortisone and ACTH in a boy diagnosed as suffering from Hand-Schüller-Christian syndrome when 1 year old, the symptoms having commenced about four months previously. After a year's treatment with cortisone followed by ACTH, maximum dosage 75 mg. daily, he developed marked features associated with Cushing's syndrome at which stage treatment was gradually reduced; but bone lesions which were already resolving continued to improve and eventually disappeared after four years' treatment.

Bearing this evidence in mind, it is necessary to remember the occurrence of spontaneous remission which is the usual outcome in patients with eosinophilic granuloma of bone and is also well recognized in the Hand-Schüller-Christian syndrome.

Moreau (1930) found nine cases of spontaneous recovery amongst 34 cases of Hand-Schüller-Christian syndrome described in the literature, and while Letterer Siwe disease is generally fatal, spontaneous recovery is possible (Lightwood and Tizard, 1954). Recovery from this disease induced by cortisone was described by Cox (1955), and Orrild and Lunding (1953) reported a case of Letterer Siwe disease apparently cured by ACTH.

The object of this communication is to place

on record two further cases of reticulosis and to describe the effect of prolonged steroid therapy in one, the other dying before treatment was properly instituted.

### Case Reports

**Case 1.** J.E. was 25 months of age when admitted to hospital in April, 1955, with a history of malaise following an upper respiratory infection two weeks previously. For a week he had been drowsy and listless, inclined to vomit and was thought by his mother to be having headaches. A few days before admission puffiness was noticed around the eyes, which for the past 24 hours had protruded.

He was the second child of healthy parents, born at term; his birth weight was 7 lb. 11 oz. He was breast fed for one month only, but he made good progress and his only illness had been an attack of otitis media treated with penicillin one year previously. The family history was uneventful.

EXAMINATION. Temperature 99·8°F. He had a pale, puffy face and proptosis of both eyes, the right slightly more than the left. In addition to the puffiness of the eyelids there were also symmetrical, fairly well defined swellings in the temporal fossae (Fig. 1) and an indefinite swelling in the right parietal region. The tonsils were enlarged but not inflamed; cervical and axillary glands were moderately enlarged; the heart and lungs appeared normal; liver and spleen were not felt. The optic fundi showed no abnormality, and the cerebrospinal fluid was also found to be normal. A blood count was reported Hb 86% (12·7 g.); colour index, 1·04; W.B.C.s, 6,000/c.mm. (polymorphs 40%, lymphocytes 60%).

A tentative diagnosis of Hand-Schüller-Christian syndrome was made, but there was no polyuria and urine specific gravity reached 1,016. Moreover, radiographs of skull, thorax and long bones revealed no abnormality apart from opacity of both antra and ethmoid cells. Because of this finding and the fact that his temperature fluctuated between 100° and 101° F. the possibility of ethmoiditis was considered, and treatment with antibiotics started. No improvement followed, however, and six days after admission chemosis of both conjunctivae and retinal oedema appeared; there was no real papilloedema. A second blood count showed a fall in Hb to 78% (11·5 g.) and vacuolated cells were found in the smear (Fig. 2). The E.S.R. was 6 mm. in one hour, platelets 14,000/c.mm. and bleeding time more than 12 minutes. Bone marrow aspiration showed a normocellular marrow containing 'foam cells' (Fig. 3) simila-

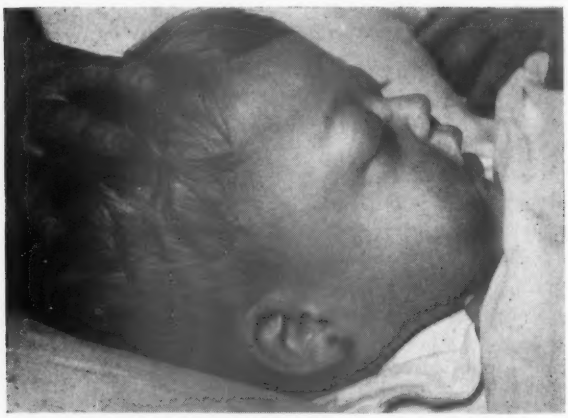

FIG. 1.—Showing puffiness of eyelids and symmetrical well-defined swellings in temporal fossae.

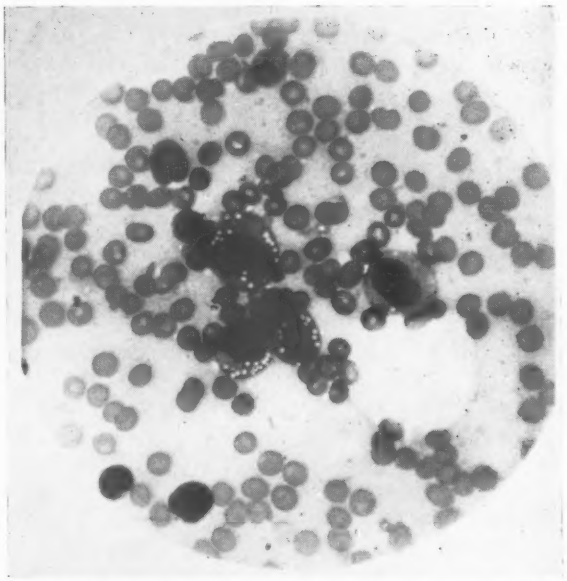

FIG. 2.—Blood smear showing vacuolated macrophages. (×480.)

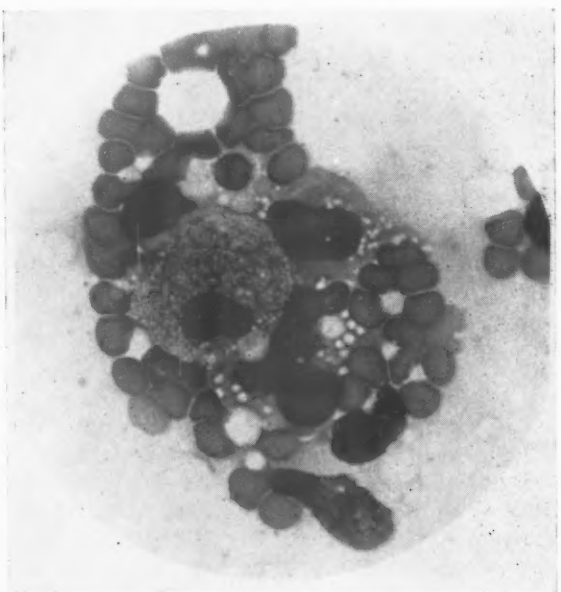

FIG. 3.—Bone marrow showing a foam cell and vacuolated cells. (×650.)

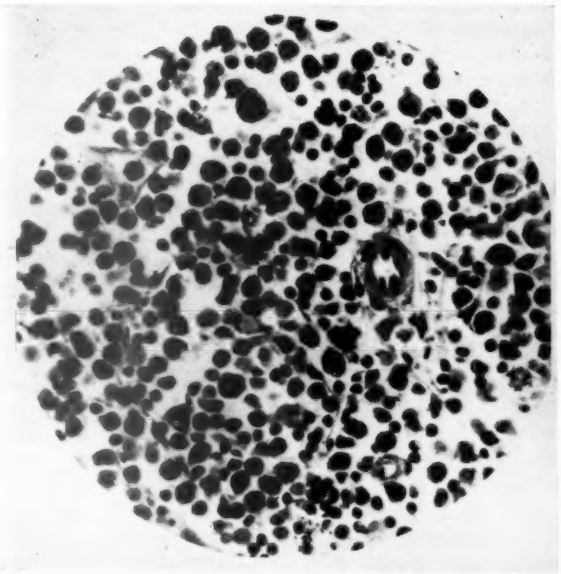

FIG. 4.—Gland infiltrated with reticulum cells. (H. and E. × 150.)

FIG. 5.—Horizontal section through skull showing tumour-like mass in anterior fossae.

those occurring in the Hand-Schüller-Christian syndrome; gland biopsy showed complete replacement of the normal architecture by sheets of pale reticulum cells, but no 'foam cells' (Fig. 4).

Cortisone was now added to the treatment but the child's condition deteriorated rapidly. Spontaneous bleeding occurred and he became progressively more anaemic in spite of blood transfusion.

He appeared to be quite blind for several days before he died, two weeks after admission to hospital.

NECROPSY. A mass of tumour-like tissue in the anterior fossae of the skull, in the orbits and air sinuses, and invading the upper part of the nose via the cribriform plate was revealed (Fig. 5), but the pituitary fossa appeared intact. A large tumour was found in the lower end of the right femur (Fig. 6). The thoracic and abdominal glands were all enlarged and invaded, and there were small deposits in the heart, kidneys and wall

FIG. 6.—Large tumour in lower end of right femur.

of the small intestine. The liver and spleen appeared normal macroscopically and the lungs showed hypostatic changes only, but histological deposits were noted in lungs, spleen, liver, pancreas, ribs and tonsils. The pituitary gland was normal on section apart from tumour around the capsule. The microscopic picture was of uniform infiltration with sheets and trabeculae of mononuclear cells with pleomorphic nuclei and scanty eosinophilic cytoplasm. No foam cells were found in any of the necropsy sections and no cholesterol was demonstrable in the cells by histochemical techniques.

**Case 2.** J.C. was 5 years old when admitted in February, 1957, with a history of malaise, loss of appetite, limb pains and irregular fever following an upper respiratory infection one month earlier. He was the third and youngest child of healthy parents, born at term; his birth weight was 6 lb. 10 oz. He was breast fed for three months and his progress had been entirely normal. The family history was uneventful.

EXAMINATION. He was a fretful, pale, ill-looking child, with several small bruises and a few petechiae on the trunk. His tonsils were large and unhealthy and tonsillar glands were palpable; there were small discrete glands in axillae and groins, and his liver was easily palpable, his spleen being just felt. No nodules or bony swellings were found, but he resented examination because of muscle tenderness. A tuberculin patch test was negative. Radiographs showed possible erosion of one rib, but no lesion in skull, spine or long bones. Haematological examination revealed Hb 64%, W.B.C.s less than 1,000/c.mm. (polymorphs 11%, lymphocytes 87%, monocytes 2%, platelets scanty); bleeding time more than 15 minutes. Marrow puncture demonstrated the presence in the marrow of many histiocytic cells with slightly foamy cytoplasm, suggesting a diagnosis of Letterer Siwe syndrome. ACTH in a dosage of 40 units daily was started four days after admission together with penicillin, and a blood transfusion was given the following day, Hb having fallen to 58%; a blood film at this time showed many smear cells.

After four days' treatment the child's general condition had improved remarkably; he lost his muscle pains and became much more cooperative, accepting drugs by mouth which he had previously refused, so prednisolone 12·5 mg. t.d.s. was substituted for ACTH intramuscularly. He was given another blood transfusion as his Hb had only risen to 66% and four weeks after the beginning of treatment he was symptom-free, had no palpable glands, no obvious enlargement of the spleen and a second marrow puncture showed a normal picture apart from a very few of the abnormal cells originally seen. His liver, however, was still palpable two finger breadths below the costal margin. He had become moonfaced, and his weight had increased by 8 lb. over his admission weight of 29 lb. 5 oz., so prednisolone was reduced to 10 mg. t.d.s. and on this dosage he was discharged to the Out-patient Department at the end of March, his Hb at that time being 75% and W.B.C.s 4,600/c.mm. Dr. Bodley Scott who had seen this child in consultation reported: 'I agree that the primitive cells found in the bone marrow and displacing almost all the normal cells are quite unlike the usual 'blasts' of acute leukaemia. They have irregular nuclei of the reticulum cell type and some have a foamy cytoplasm. Together with the x-ray changes they support a diagnosis of 'Letterer Siwe syndrome'.'

He was seen frequently in the Out-patient Department and he remained well but exhibited the appearance of florid Cushing's syndrome. His haemoglobin was maintained and he had no enlargement of liver, spleen or glands. He complained of pain in one ankle but nothing abnormal was found, and as he was markedly overweight (46 lb.) his dose of prednisolone was reduced slowly after two months on 30 mg. daily, until he was taking only 5 mg. a day at the beginning of July. He lost 5 lb. in weight, felt well and began to grow. His Hb was still 96% and blood picture normal; B.P. 110/65 mm. Hg. Prednisolone was again reduced in August to 2·5 mg. daily and continued at this level until in September his testes were noticed to be rather hard and insensitive, and a week later his parotid, submaxillary, axillary and inguinal glands were visibly enlarged and felt firm. Liver and spleen were still not palpable and Hb was 90%, but smear cells were again seen in the blood film (September 24, 1959), as well as a few atypical mononuclear cells. He was admitted on October 1, 1957, for biopsy of a gland and the dose of prednisolone was increased to 10 mg. daily, but he did not improve. The report on the biopsy specimen stated: 'The normal structure of the lymph node has been destroyed, being replaced by a uniform proliferation of medium sized oval cells with scanty eosinophilic cytoplasm and reticular nuclei. The capsule is invaded at one point, and the abnormal cells are infiltrating the fat outside the node. Mitoses are numerous. I regard this tumour as a lymphosarcoma.'

Prednisolone therapy was continued in the same dosage but muscle pains returned and a few histiocytic cells were again seen in the peripheral blood in mid-October, at which time the dose was increased to 30 mg. daily. Rapid weight gain resulted but the symptoms progressed and by the middle of November he was unable to walk on account of general stiffness and tenderness. Radiographs of ribs, pelvis and long bones (November 15, 1957) showed no abnormality.

His condition deteriorated steadily, he became anaemic and leucopenic once more, and developed scattered bruises and petechiae. His weight fell steadily to 36 lb. on December 10, in spite of progressive increase in the dose of prednisolone up to 120 mg. daily and blood transfusion, and by December 20, 1957, his liver had enlarged to three fingers-breadth below the costal margin and spleen and glands were easily palpable. Radiographs (December 19, 1957) showed a little periosteal infiltration in several long bones and slight generalized osteoporosis. He was discharged home for Christmas and re-admitted (December 30, 1957) in severe pain, extremely weak and bleeding from the nose; Hb 40%, W.B.C.s too scanty to count. He was again transfused and another bone marrow puncture was attempted, but

was unsuccessful because he bled too much. For the same reason biochemical investigations were not undertaken, but on January 3, 1958 potassium chloride 1·5 g. daily by mouth was started on an empirical basis because of high dosage of prednisolone, general weakness and abdominal distension, steroid therapy being maintained unaltered.

A few days later he was much improved, moving his legs without pain and no longer bleeding spontaneously. At the beginning of February he was once more on his feet, and even running a little. His haemoglobin rose steadily without further transfusion, his white cell count became normal and no histiocytes or smear cells were seen in the blood film; his spleen was no longer palpable but his liver and preauricular glands were just felt.

He was discharged home on February 12, 1958, still on 120 mg. prednisolone daily, and he felt well, but he ate enormously and gained nearly a stone in weight in the next three weeks, reaching 50 lb. His blood pressure rose to 150/90 mm. Hg, having been around 110/60 mm. Hg previously. By the end of March he was too tired to walk and complained of pain in the back, so he was readmitted on March 21, 1958, still with all the signs of florid Cushing's syndrome (Fig. 7). Radiographs showed marked osteoporosis of lumbar vertebrae with flattening and compression of most of the vertebral bodies (Fig. 8) and also slight deformity of the neck of the left femur. Apart from his high colour, obesity and loss of lumbar curve the child seemed well and showed no sign of the original disease. There was now no

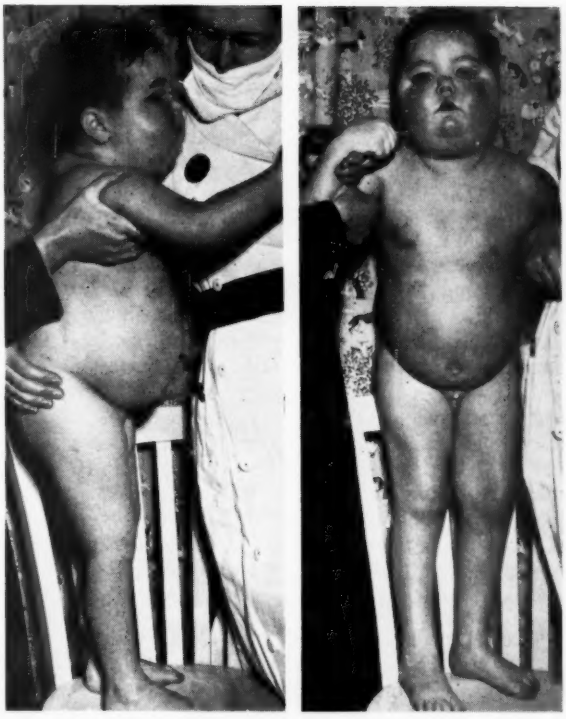

FIG. 7.—Showing signs of florid Cushing's syndrome.

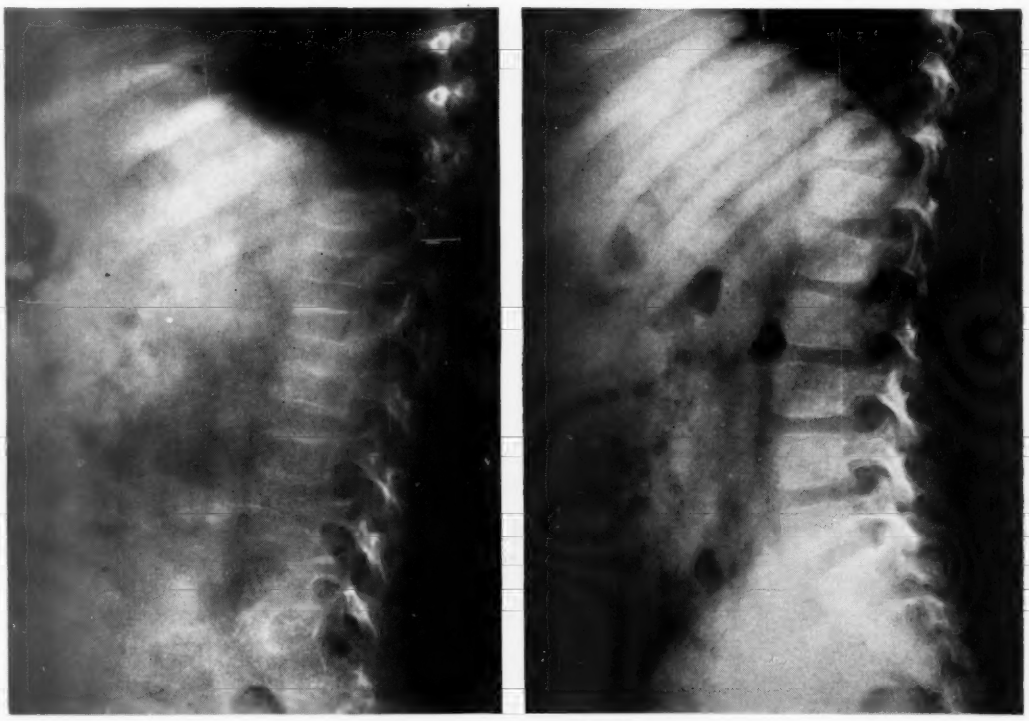

FIG. 8.—Lumbar spine showing osteoporosis, compared with spine of same patient six months earlier.

anaemia and marrow puncture showed no evidence of any haemopoietic disorder, normal polymorphs being most plentiful, granulocyte precursors numerous, primitive and abnormal cells absent.

He was fitted with a plaster bed and his dose of prednisolone was gradually reduced being combined with ACTH. He appeared well; ketosteroid excretion was satisfactory and blood pressure 120/90 mm. Hg. On May 7, on a dose of prednisolone 20 mg. b.d. and ACTH 40 mg. daily, he was found to have a number of large, slightly tender glands in the neck and a nodule on the occiput, but liver and spleen were still not palpable. On May 12 another marrow biopsy was obtained which showed the marrow grossly infiltrated by large pleomorphic reticulum cells (Fig. 9) the nuclei of which had a coarse chromatin pattern and single prominent pale blue nucleus, the picture being that of reticulum cell reticulosis. A few days later he began to deteriorate rapidly, ecchymoses appearing in the vicinity of the enlarged glands, and liver and spleen enlarging progressively. He became rapidly more anaemic in spite of blood transfusions and died suddenly on June 5, 1958, nearly 18 months after the onset of his first symptoms.

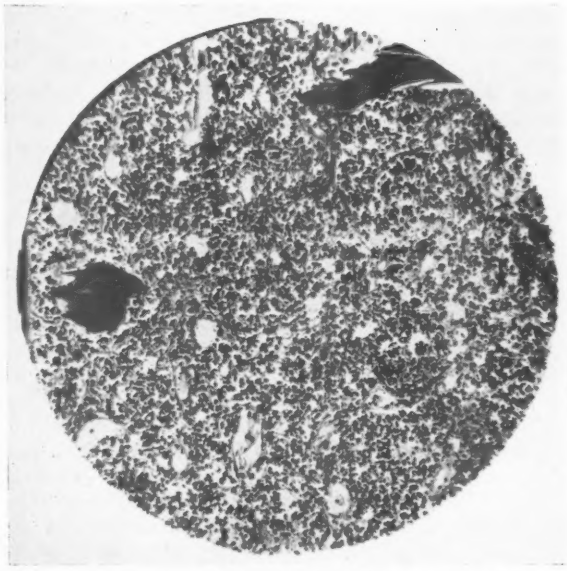

FIG. 10.—Bone marrow showing diffuse infiltration. (H. and E. ×90.)

NECROPSY. This was performed 24 hours after death. The body was that of a fat boy with the moon-facies of cortisone overdosage, showing massive ecchymosis of the left arm and lower abdominal wall, and numerous small bruises scattered over the rest of the body. There was general enlargement of lymph glands, the tracheobronchial, mediastinal and pre-aortic abdominal glands being dark red in colour and soft. Petechiae were present on the surface of the heart (which was otherwise normal) on the pleura, and in the gastric mucosa. Fresh blood was present in the small intestine, which appeared normal in other respects. The liver was of average size (870 g.) and was pale. The spleen was enlarged (180 g.) and deeply congested; other organs appeared normal. The cortex of all vertebral bodies and of the long bones was extremely thin and the marrow was dark red and prolific.

HISTOLOGY. Sections of spleen, lymph nodes and bone marrow (Fig. 10) showed replacement of the normal tissue by sheets of pleomorphic reticulum cells. The liver showed subcapsular and portal tract proliferation of these abnormal cells (Fig. 11), but the changes

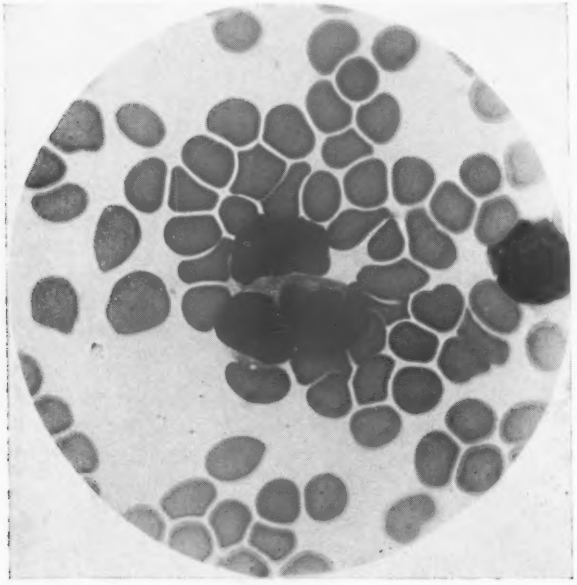

FIG. 9.—Bone marrow showing reticulum cells. (×915.)

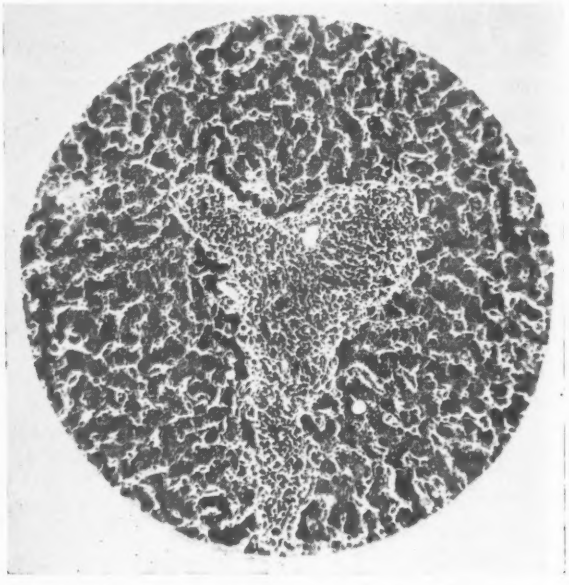

FIG. 11.—Liver showing infiltration of portal tracts. (H. and E. ×9[illegible].)

were not intense. There was no evidence of lipoid storage. The infiltrating cells varied in size and shape, some being rounded, some polygonal and others elongated. Mitoses were scanty, reticulum production slight, but the cells stained with metallic stain and some showed evidence of erythrophagocytosis.

## Discussion

Diagnosis undoubtedly depends on the histological interpretation of the type of abnormal cell seen in the marrow biopsy and necropsy sections. Cases of the type just described have been published under various names, but the unifying feature is a diffuse infiltration of the marrow by cells of reticuloendothelial type. The two cases under discussion fulfil the clinical criteria advanced by Siwe, but at the same time show certain points of dissimilarity.

Case 1 had marked exophthalmos and foam cells in the marrow biopsy, but the classical triad of the Hand-Schüller-Christian syndrome was lacking. The rapid course of the disease in this case was characteristic of Letterer-Siwe syndrome, though the biopsy picture was more suggestive of the term acute xanthomatous reticuloendotheliosis.

Case 2 conformed more closely to the conception of a malignant reticuloendotheliosis, which was probably what the original authors described as Letterer-Siwe disease, but which in his case was checked over long periods by steroid therapy.

These two cases support a contention made by Lynch, Bain, Stanyon and Crang (1954) that two different disease entities are often confused under this eponym. That steroids influence all varieties of reticulosis there is no doubt; but the possibility of spontaneous remission must not be forgotten. The response to steroids accentuates neither the relationship nor the diversity of the pathological forms.

## Summary

Two cases of reticuloendotheliosis of Letterer-Siwe type are described, and the effects of prolonged steroid therapy indicated. A brief review of the literature in relation to steroid therapy of the reticuloses is included.

I am greatly indebted to Dr. J. L. Hamilton-Paterson who performed the autopsies and supplied the pathological reports, to Dr. R. Bodley Scott who saw Case 2 in consultation, and to Miss M. H. Shaw for the photographs.

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# A CASE OF SEVERE HYPERCALCAEMIA OF INFANCY WITH AN ACCOUNT OF THE NEUROPATHOLOGICAL FINDINGS

BY

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Hypercalcaemia of infancy has been divided into severe and simple or benign forms, each with distinct clinical pictures. However, Joseph and Parrott (1958) considered that the two forms were different degrees of severity of the same disease. Forfar, Tompsett and Forshall (1959) thought that the severe form, which tends to be recognized later in infancy, was the result of delay in diagnosis.

The severe form, which according to Fellers and Schwartz (1958) is 14 times less common than the simple form, was first described by Fanconi, Girardet, Schlesinger, Butler and Black (1952). Amongst its multiple symptoms and signs are dwarfism, mental retardation, persistent hypercalcaemia, hypercholesterolaemia, osteosclerosis and evidence of renal disturbance with albuminuria and nitrogen retention. The prognosis is poor. By contrast, the simple form first described by Lightwood (1952) is unassociated with mental deficiency and osteosclerosis and has a good prognosis.

Several workers have described the visceral changes, particularly renal, in severe hypercalcaemia, but neuropathological findings have not been hitherto reported. The object of this communication is to record a case which came to autopsy and had a full pathological examination.

## Case History

The patient, the first born of healthy parents, the mother 18 and the father 37 years of age, with no family history of mental or neurological illness, was delivered normally after a labour lasting 44 hours. The pregnancy was normal. He weighed 9 lb. 6 oz. (4,220 g.) at birth and his head circumference of 14½ in. (36·8 cm.) was of normal size. He had a capillary-cavernous 'strawberry' naevus on the outer side of the right elbow ⅞ in. (2·2 cm.) in diameter and a similar lesion ⅝ in. (1·6 cm.) in the left deltoid region.

At first he progressed normally but on the 3rd day he had a cyanotic attack and was given oxygen. Later the same day he had several tonic convulsions with opisthotonus and flexion of all limbs, each attack lasting about two minutes. Cerebrospinal fluid was clear and xanthochromic with a protein content of 300 mg. % and a normal cell count.

He was weaned on to half-cream national dried milk at 17 days and changed gradually to full-cream milk at 12 weeks. One teaspoonful of cod liver oil was given daily. He was a slow feeder, often vomited and was constipated. These features persisted throughout life.

The cutaneous naevi increased in size up to the 4th month after which they became stationary. At this time his head circumference, 15⅞ in. (40·2 cm.), was within normal limits. At 5 months his blood pressure was 124/76 mm. Hg and radiography showed normal bone development and calcification of hands and feet. Convulsions, consisting of sudden jumps, stiffness of the arms and legs, and cyanosis continued. Although some measure of control was achieved by sedation he sometimes had several attacks a day. At 9 months he was considered to be mentally retarded, deaf and blind with optic atrophy.

While in hospital from 11 months to 2 years and 3 months weight gain was satisfactory in spite of feeding difficulties and intercurrent respiratory infections. The fontanelles closed normally but his head size increased very slowly and at 2 years the circumference was 16¾ in. (42·6 cm.). His pupils did not react to light and he had slight nystagmus. The discs were small and pale but the retinae were normal. All limbs were hypertonic and the reflexes brisk. Plantar reflexes were extensor. The Mantoux 1/1,000 and toxoplasmin skin tests were negative. Marrow and blood counts were normal.

Many chemical investigations were carried out during the first 2 years of life. The blood urea was raised between 60 and 82 mg. %. Calcium in the blood varied from 11·3 to 16·6 mg. % (the diagnostic level given by Stapleton and Evans (1955) was 12·5 mg./100 ml.). Blood phosphates were between 5·5 and 9·9 mg. %; plasma protein 7·0 to 7·3 mg. %; serum cholesterol 293 mg. %. The alkaline phosphatase in six estimations varied between 15·7 and 28·4 King Armstrong units/100 ml. but there was a seventh estimation in which it was 5·4 units/100 ml. The $CO_2$ combining power was 30·8 mEq./litre. The $I^{131}$ excretion test was normal.

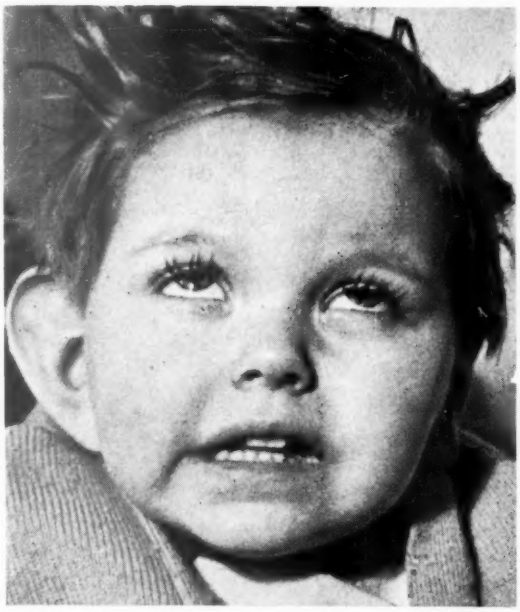

FIG. 1.—Rounded face with eyes set wide apart, epicanthic folds and large low-set ears.

Paper chromatography revealed a normal amino-acid urinary excretion. C.S.F. protein returned to normal towards the end of the first year.

He was admitted to the Fountain Hospital at the age of 2 years and 3 months when he was found to be an idiot behaving like a 2-month-old baby, requiring three-hourly bottle feeding. He could not talk, sit, stand, walk, nor even lift his head. He showed no apparent interest in his surroundings and rapport could not be established. His weight was 22 lb. and head circumference 16¾ in. (42·4 cm.) (normal is 49·7 cm.).

FIG. 2.—Two small foci of calcification in the first premolar.

His face was round with eyes set wide apart, epicanthic folds were present and the ears were large and low-set (Fig. 1). He lay in a curious 'frog' position, the legs abducted at the hips and maintained rigidly in a flexed position. There was spastic diplegia.

Two weeks after admission to the Fountain Hospital, he developed a pyrexial attack (103 to 105° F.) with haemoconcentration and a leucocytosis of 20,000. Choreic movements of the face and limbs, head retraction and arching of the back occurred. Excitement and screaming attacks were frequently present and he often slept during the day and was sleepless at night. When asleep his movements ceased. The cause of his illness, which persisted intermittently till death seven months later, was obscure, in spite of many investigations. These excluded meningitis, middle-ear disease and other infections. A moderate degree of papillitis lasting about six weeks was noted. C.S.F. protein increased to 90 mg.% with a slight increase of globulin but other constituents were normal. Dr. Frank Elliott suggested that the cause of these symptoms and signs might be naevoid amentia with naevoid malformation at the base of the hypothalamus and pons, a diagnosis of some significance in view of subsequent findings. Radiography of the skull and spine at 2 years and 5 months revealed generalized osteosclerosis and two foci of calcification in the pulp of a deciduous premolar (Fig. 2).

He died from broncho-pneumonia at the age of 2 years and 10 months.

When the child was 10 months old the parents had a second infant, a girl, who developed normally and at 8 years was fit and well.

**Pathological Findings.** At necropsy performed on the day of death, the body was found to be well nourished. However, comparison with Coppoletta and Wolbach's (1933) tables of organ weights of infants and children revealed that his stature of 81 cm. (normal 88 cm.) was stunted and the weights of his heart, lungs, spleen, liver, kidneys and brain were all lighter than the average for his age. His head circumference was 42·6 cm. (normal 50·4 cm., S.D. = ±1·35 cm.). He was therefore microcephalic.

Foetal lobulation was present in both kidneys (left 35 g., normal 49 g.; right 30 g., normal 48 g.), each of which showed longitudinal yellowish streaking of the medulla. Atheromatous deposits encircled the commencement of the aorta. The heart was well formed.

The brain, symmetrical in shape and covered by clear leptomeninges, weighed 825 g. (normal 1,140 g.). It was very soft at the time of removal and, with convolutional flattening, was considered to be oedematous. The olfactory and optic nerves appeared small but other cranial nerves were normal. Attached to the caudal part of the optic chiasma and anterior part of the tuber cinereum and chiasma and the hypophysis cerebri, was a soft grey nodule 4 mm. in diameter (Fig. 3). Basal vessels were normal. There were no naked eye abnormalities of the spinal cord.

**Histological Findings.** Coronal sections of the frontal, temporal and occipital lobes, the basal ganglia, mid-

FIG. 3.—The small rounded infundibuloma arising from the floor of the third ventricle and anterior part of the hypophysis cerebri.

brain, pons, medulla, cerebellum, cervical, thoracic and lumbar cord were embedded in celloidin and sections stained by the usual neuropathological procedures—Nissl, Heidenhain, H.V.G., Mallory's P.T.A.H. and Holzer techniques. Paraffin embedding was carried out on the optic nerves, cortex and viscera and sections were stained by the H.V.G., H. and E., P.T.A.H., Gl es Marsland and Loyez methods. Frozen sections of the cortex were used for Holzer, von Kossa and Scarlet R. methods.

The gyri were well formed but lamination within their grey matter was often indistinct and there was a generalized sparsity of nerve cells especially in layer III. Betz cells, looked for in many blocks, were absent from the motor cortex. The striate cortex could not be identified with certainty. Perigyral gliosis was increased in some areas, notably in the frontal, parietal and occipital lobes. The white matter was well medullated. However, it contained many ectopic nerve cells e.g. in the corona radiata there were five times more nerve cells than in an equivalent area of the brain of a mature newborn infant and 30 times more cells than in the brain of an infant of 1 year.

Apart from focal increases in Bergmann's cells, the cerebellum was well formed.

The nodule behind the chiasma was formed of glial cells and capillaries (Fig. 4). Most of the glial cells had round or oval nuclei with well-defined nuclear membrane. The nuclei contained powdery particles and two or three larger chromatin nodules. A few cells were smaller and hyperchromatic. The cells were arranged rather loosely except near the blood vessels where they were

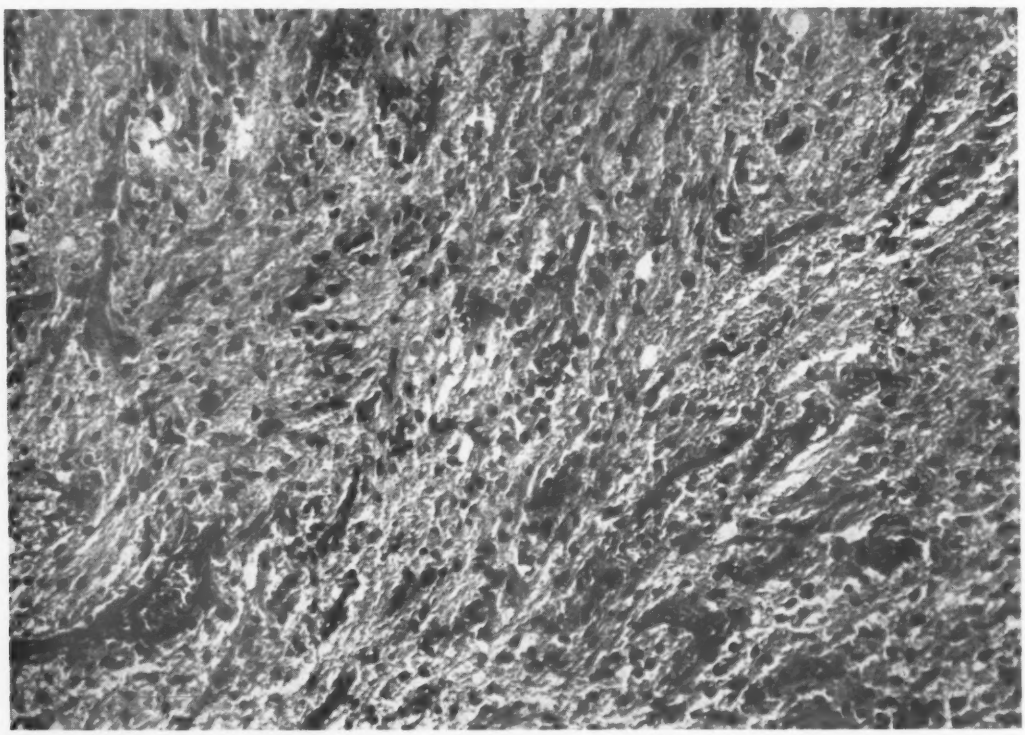

FIG. 4.—Rather haphazard arrangement of glial cells in the infundibuloma had a tendency to more compact arrangement around the vessels. (H. and E. ×156.)

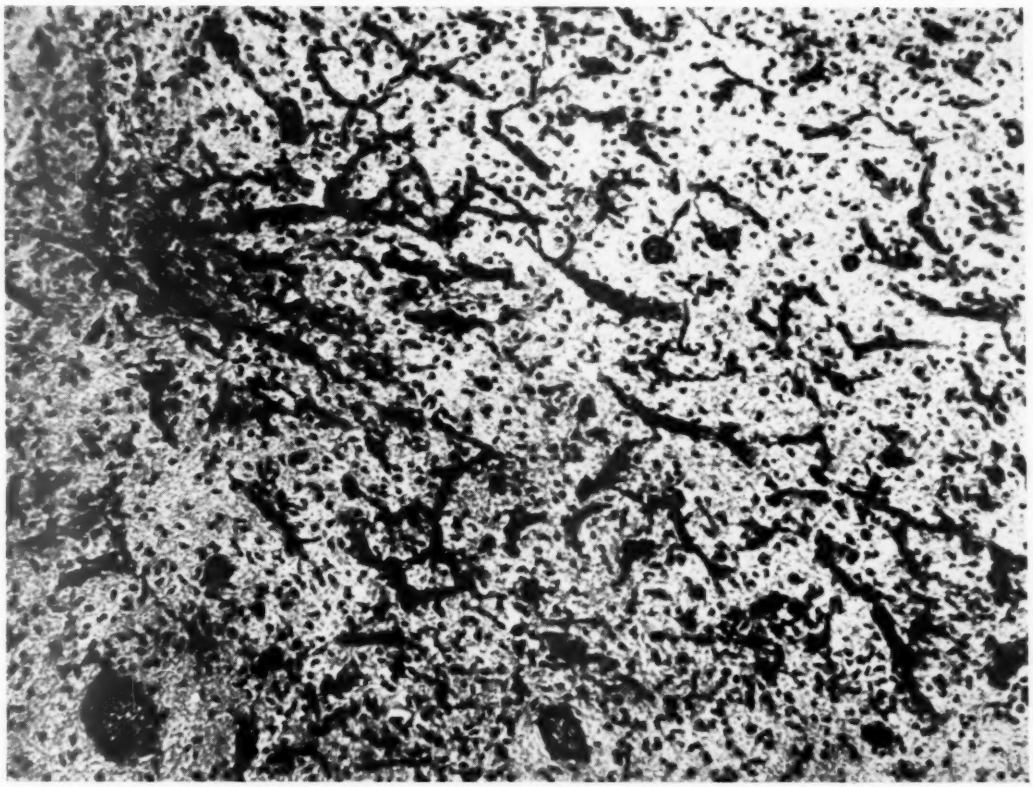

FIG. 5.—Collagenized capillaries, most of them bloodless, and inter-capillary gliosis in the cortical naevus (H.V.G. ×162.)

denser. Their fine fibrils formed a delicate open network with occasional microcysts in the H. and E. and H.V.G. preparations. In the Holzer sections there were a few thick sturdy looking angulated fibres. Blood vessels were looped into several coils and contained an excess of reticulin in their walls. This gave them a bizarre glomerular-like appearance. There were neither multinucleated giant cells nor mitotic figures. A few globoid eosinophilic colloidal bodies or droplets were present.

A vascular naevus was found in the grey matter of the parietal lobe in the vicinity of the Rolandic fissure when this was sectioned. Situated in the grey matter bordering a sulcus, it measured approximately 1·5 mm. in length and involved layers I, II and III (molecular, external granular and pyramidal cell layers). It consisted of a network of collagenized capillaries (Fig. 5). Only a few of the capillaries contained red cells. Elastic tissue was not seen in their walls. Glial cells were numerous throughout the area. A dense feltwork of glial fibres was arranged in a racemose fashion around the periphery of the lesion, from which many branches invaded neighbouring grey matter. There were neither saccular nor fusiform dilatations. Calcification was absent.

Numerous calcareous deposits were situated chiefly in the outer half of the pyramids of the kidneys with occasional foci in the medullary rays. Interstitial fibrosis was present around these foci and ischaemic changes were seen in some glomerular tufts. It was often difficult to identify the precise site of the calcified structures because of distortion by fibrosis. Many were large enough to be seen by the naked eye (like grains of black pepper in the von Kossa preparation); for instance, some of the larger deposits were contained within a thin lining of fibrous tissue and it was impossible to say whether they originated within the lumen of a tubule, in its epithelium or in the interstitial tissue. These large deposits compressed surrounding tubules. The smaller deposits were also difficult to place, but some appeared to have formed below the level of the tubular epithelium which they had dislodged towards the lumen. Many smaller deposits appeared to be interstitial.

Glomerular changes were focal and included shrinkage of the capillary tufts with hyperchromasia of nuclei. Fibrous tissue was increased around some Bowman's capsules and the interstitial tissue contained an excess of fibrocytes and round cells. There were no polymorphonuclear cells; there was no calcium-like deposit in the glomeruli or adjacent tissue and blood vessels were normal.

The available sections of the pituitary gland were small when compared with a gland from a child of similar age. Apart from congestion of the sinusoids it appeared normal structurally. Atrophic changes were conspicuous in the thymus and included smallness of lobules with

poor differentiation between cortex and medulla; Hassall's bodies were calcified and there was a great deal of fibrous stroma and fatty infiltration. There was infiltration of the portal tracts by small round cells. Broncho-pneumonic changes were confirmed in the lungs. Other viscera appeared normal.

## Discussion

The hypercalcaemia and the clinical features of mental deficiency, osteosclerosis and stunting made it reasonably certain that this boy suffered from a severe form of hypercalcaemia of infancy. Failure of the skull to grow adequately after birth and the development of osteosclerosis signified the progressive nature of the disease. Nephrocalcinosis, found in both forms of this disease, was also present and the renal lesions were similar to those described by Dawson, Craig and Perera (1954), Rhaney and Mitchell (1956), and Shanks and MacDonald (1959) Type III lesion. An unusual feature was foci of metastatic calcification in the pulp of a deciduous premolar. Dawson *et al.* (1954) found similar lesions in a lower deciduous incisor.

Micrencephaly, poor lamination of nerve cells and universal paucity of nerve cells in the grey matter especially in layer III (pyramidal cell layer) were severe enough to account for the mental deficiency in this boy. The paucity of cortical nerve cells could probably in part be due to the excessive number of ectopic nerve cells in the white matter indicating a failure in the normal migration of neuroblasts towards the pallium, either in the later months of pregnancy or early in infancy. Clearly, with the early onset of convulsions and initially raised cerebrospinal fluid protein there was evidence that the disturbance of the nervous system was already present in early infancy. It is also impossible to exclude the possibility of ictal neural damage.

Rhaney and Mitchell (1956) reported medial calcification of the middle cerebral artery within the basal ganglia in a child of 10 months whose brain weight was normal and who suffered from the mild form of the disease. The vessels in this child were free from this abnormality.

The tumour situated between the optic chiasma and hypophysis cerebri had many of the features of an infundibuloma; a condition recently reviewed by Wolman (1959). Its situation invites speculation into the effects it may have had on the child's metabolism and physical state. As indicated in the history, a lesion of the hypothalamus was suspected in life. Diabetes insipidus was not present. Although he was well nourished, he was not excessively fat and his genital organs were quite well developed, there being thus no signs of adiposo-genital syndrome. As a matter of interest and by contrast, Kagan (1958) described a large tumour of the third ventricle, regarded as an astrocytoma in a 5½-month-old infant in whom the blood calcium was normal and the main features were anorexia and inanition.

The histological character of the vascular naevus did not fit easily into Russell and Rubinstein's (1959) classification of capillary telangiectasis, cavernous angiomas and venous and arteriovenous angiomas. It resembled most a racemose venous naevus composed of small channels. However, a pia-arachnoid component was not demonstrated and the lesion in this child was within the substance of the brain. Corrin (1959) stated that cavernous angiomas were similar in structure to the common cutaneous angiomas and that occasionally they were associated with angiomatous lesions of the skin and other organs. Unfortunately, the skin lesions were not examined histologically.

It was impossible to decide whether the hypercalcaemia was causally related to the naevoid anomalies and the infundibuloma or was a fortuitous complication such as might have arisen from some fault in the early feeding involving calcium and vitamin D or hypersensitivity to vitamin D; causal factors which have recently been discussed by Bonham Carter, Dent, Fowler and Harper (1955), Morgan, Mitchell, Stowers and Thomson (1956), Fellers and Schwartz (1958), and Forfar *et al.* (1959). Nevertheless, it could not be ruled out that the more economical explanation of a single cause such as a biochemical defect manifested itself as localized faults of morphogenesis.

## Summary

An epileptic microcephalic idiot boy was stunted and had spastic quadriplegia, capillary-cavernous naevi of the skin and hypercalcaemia and osteosclerosis of the skull. Pathologically, there were micrencephaly, generalized paucity of nerve cells in the grey matter and an excessive number of ectopic nerve cells in the white matter, a gliosed vascular tumour of the left cerebral cortex and an infundibuloma.

Our thanks are due to several colleagues at the Fountain Hospital and the Postgraduate Medical School who supplied information.

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# BOOK REVIEWS

**Atrial Septal Defect.** By H. GÖSTA DAVIDSEN. (Pp. 225; 347 refs; 49 figs; 12 tables. D. kroner 50.00.) Copenhagen: Munksgaard. 1960.

Accurate information concerning the natural history of disease is as elusive as it is important, for without this knowledge rational treatment can hardly be said to exist. In attempting to set down the story of atrial septal defect Dr. Davidsen has clarified the background against which the treatment of this anomaly must be set. Although most of the 225 paper-backed pages are taken up with the minutiae of a thorough, careful and painstaking study of 15% of the atrial septal defects in Denmark, being a series of 132 patients seen at the Rigshospitalet, Copenhagen, considerable space is devoted to an analysis of the 190 autopsy reports in the literature. These latter records are admittedly unrepresentative, but they are unique, as they antedate the era of operative treatment and from them the author has extracted an amazing amount of information. In 68 of the 132 patients of Copenhagen the diagnosis of heart disease was made before the age of 7 years. The subject is presented well in eight chapters with excellent summaries of each. From the gravity of the late prognosis in atrial septal defect, the author concludes that there are sufficient grounds for attempting an improvement in the prognosis by surgical treatment. Such treatment should be carried out before irreversible changes have occurred in the pulmonary vessels and cardiac valves. The scope of the book excludes the technique or results of operative treatment. In a chapter devoted to electrocardiographic changes some reference might have been made to the value of the vector cardiogram. The reproduction of radiographs is good, and the diagrams and line drawings prepared by the author himself are commendable. Full references are given to the 347 publications quoted and the index is accurate if a trifle curtailed. Spelling mistakes are few for a book published in a language 'foreign' to author and printer, and the quality of print and paper is good.

**The Purpose and Practice of Medicine.** By SIR JAMES SPENCE. (Pp. x + 308; illustrated. 42s.) London: Oxford University Press. 1960.

This book is made up of a selection of 20 of the papers and lectures of James Spence, edited anonymously by his friends and colleagues. They are divided into sections entitled 'The Nature of Disease', 'The Study of Disease', 'Children and Families', 'The Care of the Child', and 'The Practice of Medicine' and the 'Training of Doctors'. The first of these sections shows the young Spence writing papers on pernicious anaemia, xerophthalmia, epituberculosis and other medical subjects of current interest in the era 1920-1933. These probably differ little from similar papers written by others at the time, but in 1934 there was published an 'Investigation into the Health and Nutrition of Certain of the Children of Newcastle upon Tyne between the Ages of 1 and 5 Years'. This work, done at the time of the great depression, marked the beginning of Spence's long and fruitful collaboration with the Health Authority of his own city, which led on to the unique 1,000 family survey, launched before his death and carried on afterwards by his collaborators. From this time, as his bibliography shows, he became less interested in clinical medicine itself, in so far as it concerns itself with particular diseases, and more and more interested in the way in which medicine should be studied and should be taught.

In turn this led on to the main concern of the latter years of his life, the institutions which men create to fulfil particular needs, and the manner in which these institutions evolve, or fail to evolve, as those needs change. He liked to regard the human family as the oldest of its institutions, and his masterly discourse on 'The Purpose of the Family' should be read in this context. His membership of the University Grants Committee brought him into close contact with the university and the teaching hospital *qua* institutions, and during the last decade of his life his interest, his talk and his energies were increasingly taken up with university policy. Unfortunately he wrote little on this subject.

The book ends with his address to the Newcastle and Northern Counties Medical Society, given a few months before his death in 1954. He spoke on Institutional Medicine, and the opening words are beautifully characteristic of his style.

> 'It is, I think, one of the inherent peculiarities of an Englishman, and more particularly of a Northumbrian, that, if you scratch him he begins to brood over his institutions. And then from time to time he reforms them. He is, as it were, still in those tremendous years before and after 1688, when our revolution was settled more by sincerity of argument than by force of arms, and when there were men of the calibre of Halifax the Trimmer to hold the balance. Now, again, in this century we are in the midst of another revolution, which is shown in our concern about our institutions. If we have neither the vigour, which is an affair of the spirit, nor the means, which is an affair of the intelligence, to reform our institutions, it will be a matter of interest mainly to the historians of the future; but such a state of affairs will be cold comfort to those of us who believe that the excellence of a civilization is shown in the capacity of its citizens constantly to reform its institutions in order to meet its changing cultural needs. But change may be for the better or the worse, and in remembering this we should be guided by Burke's admonition, that "merely to innovate is not to reform".'

The style of his prepared utterances is terse, witty and embellished with apt references to the work and words of men, past and present, whom he admired. Discussion of the present and future is characteristically based on experience to be gained from a study of history,

for his historical sense was one of his outstanding intellectual qualities. Alas, his prepared speeches, vivid though they are to read, cannot give more than a faint impression of the unforgettable delight of his conversation, nor of the effect of his extempore contributions at conference or committee. Yet it was by these means that he mainly achieved the great influence he had on his contemporaries during his lifetime. His approach to life had much of the imaginativeness of the artist about it, so that his judgments seemed to be arrived at intuitively, and his opinions often enough had a touch of waywardness about them, leading to his being apt to take an entirely unexpected line on some controversial issue. Inevitably these aspects of his personality cannot be reflected in a book made up of his formal utterances.

Yet, happily, something of the charm of his personality, of the enchantment of his companionship, and of the impact which these made upon those who knew him is brought out in the excellent Memoir (in effect a short biography) which Sir John Charles has written for this book.

All must be grateful to those who have given us this book, for James Spence was one of the two or three men whose ideas have shaped paediatrics in this country since the War.

**Cancer and Allied Diseases of Infancy and Childhood.** Ed. I. M. ARIEL and G. T. PACK. (Pp. xiii + 605; 344 figs.) London: Churchill. 1960.

This is a work of multiple authorship in which 27 contributors, all from the United States, have cooperated. The editors state that it is 'the first comprehensive treatise devoted exclusively to the clinical aspects of cancer and allied diseases in children'. The list of contributors includes names that are well known outside the United States and all are workers of experience and authority.

The scope of the book is wide. Nearly every possible type of neoplasm that may afflict children is mentioned. A liberal interpretation is given to the term 'allied diseases', a number of developmental anomalies being included which are allied to cancer only as possible problems in differential diagnosis. The principal interest of the book is surgical, although chapters are devoted to leukaemia and the 'reticuloendothelioses', which are mainly of medical interest. Some of the authors describe surgical techniques and many give details of radiotherapy. An interesting feature of many contributions is the evaluation of results of treatment culled from large series of cases in various important centres. Pathology is introduced only for the purpose of classification and to indicate the bearing of histological structure on the behaviour of tumours and consequently on treatment. No detailed pathological descriptions are given.

A few criticisms may be offered on pathological grounds. The controversial 'Ewing's tumour of bone' is accepted as a pathological entity and the frequency with which the syndrome is produced by secondary neuroblastoma is ignored. In Chapter 13 the author's attempt to resolve the existing terminological confusion between dermoid cysts and teratomata leaves the reader still confused. It is obvious that the term 'dermoid' is too widely applied. A new confusion is created by applying the term 'non-lipid reticuloendotheliosis' to Hand-Schüller-Christian disease in contrast to the diseases of Gaucher and Niemann-Pick, which are termed 'lipid reticuloendotheliosis'. This terminology is unfortunate because Hand-Schüller-Christian disease has hitherto been known as lipid reticuloendotheliosis and Letterer-Siwe disease as non-lipid reticuloendotheliosis.

It is surprising that the treatment of neuroblastoma with vitamin $B_{12}$ is dismissed in two brief sentences. In view of the encouraging results reported from Great Ormond Street Hospital, this merits more detailed consideration in a comprehensive book such as this.

The editing is good and little overlapping between contributors has been permitted. A few misprints and grammatical errors have escaped correction. The book is well produced and generously illustrated, especially with clinical photographs and radiographs. A copious bibliography is provided. The index is full but would be improved by the use of heavy type to indicate principal references among multiple entries.

**The Development of the Infant and Young Child—Normal and Abnormal.** By R. S. ILLINGWORTH. (Pp. 318; illustrated. 27s. 6d.) Edinburgh and London: Livingstone. 1960.

This is a book about the mental development of children during the first five years of life. It is not concerned with physical growth nor does it trace the mental development in specific mental diseases. The title of the book could mislead the casual reader and has rather a dull, prosaic sound about it. Not so the text. In articles published in recent years Professor Illingworth has shown great skill in portraying the social and intellectual development of young children in words readily comprehensible to paediatricians, general practitioners and lay social workers alike. In this book he has excelled himself. This is a splendid simplification and condensation of the original studies of Gesell and others adapted by the author for day-to-day clinical use and widely modified by his own large experience in paediatric practice. The reader is usually given a clear expression of opinion and many illustrative case histories are recorded. There is a wealth of good, sound, practical advice and the text includes several specimen charts for recording developmental progress which can be applied without any specialized equipment or training. There is wise emphasis upon the value of personal history-taking by an experienced clinician, though not everyone would draw quite the same conclusions from the examples quoted. There is, perhaps necessarily, a good deal of repetition in the early chapters where norms of development are discussed in the text, then classified in tables by age and then again grouped in more complex tables. The perpetual problem of deciding what is 'normal' and when behaviour becomes 'abnormal' has often been ingeniously circumvented in this book by the device of having three standards: (1) Normal, (2) Variations from Normal; (3) Abnormal.

Each chapter has an excellent bibliography and the book has a good index. It would be surprising to find no mention of autism in the index, though it receives passing mention in the text, but for the conviction that the author is really concerned with normal development and only considers abnormalities in order to illustrate how normal development can be distorted.

Chapters 5 and 12 deal with pathological development in a general fashion rather than in specific disease entities. There is a short chapter on the diagnosis of cerebral palsy and an entertaining, if not very instructive, chapter on persons of exceptional mental superiority.

The illustrations are clear and useful adjuncts to the text and there are very few misprints. There is a slight error on page 251 where two lines on electro-encephalography are allowed to intrude into discussion of pneumoencephalography and, taken in conjunction with the following sentence, might suggest that electro-encephalography is a dangerous test.

This book is entertaining and it is practical; it is very well written; it should certainly be read by all who are engaged in the study of young children and it should be purchased for permanent reference rather than borrowed from a library.

**The Physiology of the Newborn Infant.** By CLEMENT A. SMITH. (Pp. xii + 497; 62 figs. 95s.) Oxford: Blackwell Scientific Publications. 3rd edition. 1960.

The supremely high standard of previous editions of this classic study are more than fully maintained. Many chapters have been re-written. Revision has involved careful appraisal of advances made in the study of neonatal physiology since publication of the previous edition. Acknowledgements make special reference to the activities of the Nuffield Institute for Medical Research at Oxford, and the Department of Experimental Medicine at Cambridge. The format of the book remains unchanged. Each chapter consists of a scholarly evaluation of the present state of existing knowledge and prevailing views, and concludes with a summary outlining the significance and practical application of that knowledge in the clinical care of the newborn infant. Together, the richness of his personal research contributions and the wide ranging wealth of his references afford some indication of the immensity of the task undertaken by the author. With admirable skill, he marshals his evidence; from a maze of often conflicting views delineates a clearly defined theme; and with carefully developed, logical argument arrives at his assessment of the present position. Established facts are given as such. Theories as yet unproven are presented in unprejudiced form, but with an indication as to the extent to which they may be legitimately permitted to influence clinical practice. Herein is to be found one of the especial among innumerable attractions of the book to practising paediatricians. Seldom is accumulated experience and erudition available in such stimulating and readable form, as in this book. Could there be more penetrating answer to the question 'Does physiologic jaundice ever cause kernikterus, or other significant pathology?' than the author's—'The clinical problem of physiologic jaundice has heretofore been essentially a problem of differential diagnosis. It may now have become one of definition'?

**Diseases of the Nervous System in Infancy, Childhood and Adolescence.** 4th ed. By FRANK R. FORD. (Pp. xvi × 1548; 215 figs. 236s.) Oxford: Blackwell Scientific Publications. 1960.

Frank Ford's textbook, which is one of the major classics of medicine, has now reached its fourth edition. The first appeared in 1937. It is becoming increasingly rare for a single writer to attempt to cope with such an extensive field, but the result certainly has advantages in respect of uniformity of presentation and simplicity of reference. Dr. Ford's approach is refreshingly personal, thus: 'Hysterical deafness is described but I have never seen it.' In this way he avoids carrying over material of doubtful validity from previous texts. At the same time his account of the subject is very extensive and authoritative. There is no other work with which it can be compared and it is essential to any library dealing with paediatrics, neurology or child psychiatry.

The price of the book makes it unlikely to appeal to the individual purchaser though it is worth much more than a great deal of ephemeral literature. The volume is well documented and some idea of the scope can be gained from the fact that the index occupies 221 pages. The index would have been much more convenient if authors and subjects had been listed separately. The mere weight of the book makes it cumbersome for the less athletic reader; perhaps two volumes should be considered if it is to grow any more.

Dr. Ford does not give an account of the neurology of old age, but otherwise his text is so full that one wonders in what other respect it differs from a comprehensive treatise on neurology. None the less it will continue to make a special appeal to those interested in children. The revision of the new edition appears very adequate and has obviously involved critical scrutiny of recent publications. Crome's work on the neuropathology of mental subnormality is mentioned four times and a bibliography is provided in addition to references in the text. The illustrations are excellent and the quality of the paper does full justice to them.

In his section on tuberous sclerosis Dr. Ford states: 'No doubt tuberous sclerosis is frequently responsible for convulsions which are mistakenly attributed to epilepsy'. This might indicate a dualist approach, but in fact this is not reflected in the excellent chapter on epilepsy which fully recognizes the principle of causality and refers only in passing to the 'so-called essential epilepsies' as those in which 'no clinical evidence of organic disease of the brain can be found'. The author also shows a very proper scientific scepticism in regard to a special 'epileptic personality'.

It is rather surprising to find such an authority as Dr. Ford falling into the usual trap about 'mongolian spots' which he described as part of the syndrome of mongolism. Perhaps we could avoid these difficulties if we used the Russian term of 'Down's disease'! The true Mongol spot is a naevoid formation in the lumbo-sacral area,

found among Mongols and Tatars, and has nothing to do with the clinical condition of mongolism. The term 'Mongolian Idiocy' should certainly now be abandoned since, as Ford himself points out, most of these children are of imbecile level. Also, tuberculosis is no longer very common later in childhood among children with mongolism. This edition went to press too soon to record the interesting new developments in regard to chromosome constitution.

Dr. Ford has done a great service to neurology. His book is an essential work of reference in this and related fields. It will continue to be of great assistance to the practitioner, the teacher and the research worker. The English is lucid and simple.

**Infant Foods and Feeding Practice.** By HERMAN FREDERIC MEYER. (Pp. 360; 14 figs. 78s.) Springfield, Illinois: Charles C. Thomas; Oxford: Blackwell Scientific Publications. 1960.

This book, by a Chicago paediatrician, who is Associate Professor of Paediatrics at North-Western University Medical School, is most refreshing. Written by one with a long experience of routine well-baby care as well as hospital and domiciliary paediatric practice, it is the successor of 'Essentials of Infant Feeding for Physicians' which was well known in the United States a few years ago. In this volume the author has emphasized and amplified those sections of the original book which proved most popular and helpful, and the title of the book has been appropriately changed.

The theory and practice of dietetics in the first year of life, including the newborn period, are thoroughly reviewed and discussed in a very satisfying, often humorous, down-to-earth manner by one who has clearly had a great deal of experience, not only with patients but also with parents, doctors and students.

Breast feeding and its present position in paediatric practice in the United States and many other countries are fully and objectively considered, though the management of the numerous minor breast disturbances which frequently arise in the puerperium, and often unnecessarily lead to weaning, has received too little attention. The author deplores the fact that in the United States only 20% of babies are now being breast fed on discharge from maternity hospital, but he is encouraged by a reversal of this regrettable trend in the better educated sections of the community, such as university graduates.

Artificial feeding has been reviewed from its evolutionary aspect leading to the contemporary swing back of the pendulum to more fundamental, simpler methods, and the somewhat confused American scene with its 13 varieties of artificial infant foods has been arranged and coordinated into a rational picture.

The various food elements, proteins, fats, carbohydrates, minerals and vitamins, are considered in their modern context and many points which are new in a book on infant feeding attract the reader.

The section on mixed feeding is also a happy blend of the modern scientific approach and practical wisdom and experience and it is gratifying to find that the author, like most of the leading American and British paediatricians, sees no indication for introducing mixed feeding until the third or fourth month in the average infant, though it is rightly stressed that in this form of feeding, as in milk feeding, there are great individual variations.

The last chapter 'Clinical Trivia and Philosophic Observations in an Every-Day Feeding Practice' is an entertaining and intensely practical account of common misconceptions and minor problems. It will be particularly useful for students and young paediatricians and general practitioners in whose eyes some of these minor problems often loom large and may be very disturbing.

The 200 references will prove valuable for those who wish to pursue various points further. Although written for American paediatric practice this book will prove equally welcome and valuable in this and other English-speaking countries, for the basic principles of dietetics in infancy are similar everywhere.

**Neue Paediatrische Urologie.** By ERICH ZAPP. Beiheft zum Archiv fuer Kinderheilkunde, 40. Heft. (Pp. 142; illustrated.) Stuttgart: Ferdinand Enke Verlag. 1960.

In the foreword the author states that this little book is written for paediatricians in order to acquaint them with recent developments in paediatric urology. The main emphasis is on diagnosis; therapy and operations are only briefly mentioned.

The English reader will find this little monograph too short to be of much value to paediatricians; but it may be of some use to undergraduates and practitioners. It appears to be a little out of date; although written in 1960, many of the advances in paediatric urology during the last decade are not mentioned.

The first chapter contains brief descriptions of paediatric urology and diagnostic methods. It seems strange that x-ray cinematography and studies with the image intensifier, which have done so much to unravel some of the confusion surrounding paediatric urological conditions are not described at all, and that the micturating cysto-urethrogram, which is perhaps the most important of all radiological investigations in childhood, receives only scant mention.

Of the succeeding chapters, some, like the one on urinary infections and stone formation in the urinary tract, are very adequate, others, like the one on megaureters, ectopia vesicae, bladder neck obstruction and the neurogenic bladder, are somewhat out of date, especially when the treatment and indication for treatment are discussed.

It is, of course, difficult to compress such large and rapidly expanding subjects into a few pages, but it is not easy to understand why some extremely rare conditions like atresia of the urethra and congenital elephantiasis of the penis are described in some detail, and why some common lesions like phimosis and incompletely descended testicles are only very briefly mentioned.

The author has written a most readable and concise little monograph based on a comparatively small series of cases. The results mentioned in this book do not quite come up to those published by the larger Paediatric

Urological Centres in this country or the United States of America. One is therefore forced to agree with Doctor Zapp when he states that it is unfortunate that in Germany paediatric urology is not practised by specialists in this field, but remains an appendage to adult urology.

**Intussusception in Infants and Children.** By MARK M. RAVITCH. (Pp. 121; illustrated. 76s.) Springfield, Illinois: Charles C. Thomas; Oxford: Blackwell Scientific Publications. 1959.

Intussusception is still a potential killer in young children, and anyone dealing regularly with this condition will find something of interest in Mark Ravitch's book. It is the first of a new series of paediatric surgical monographs, and is based on the author's experience at the Johns Hopkins Hospital, Baltimore.

The essential theme of the book is the treatment of intussusception by barium enema reduction. As soon as the diagnosis is made, an intravenous infusion is started. An ungreased 45 ml. Foley bag catheter is inserted into the rectum, the balloon is inflated, and the buttocks tightly strapped. The catheter is connected to a reservoir of barium at a height of 3-3½ ft. above the table. Thereafter, reduction is performed under fluoroscopic control. When the ileum is seen to fill freely, reduction is complete.

This technique in Ravitch's hands is curative in 70 to 75% of all cases. When reduction is incomplete (in 25 to 30%) it is completed by open operation through a McBurney incision, thus avoiding a centrally placed scar. Using this technique at the Johns Hopkins Hospital, in the 10 years from January 1948 to January 1958, there have been 52 cases, and no deaths. Incidentally, there were only two resections.

Ravitch is convinced, by his own experience and that of other clinics using this technique, that primary reduction by hydrostatic pressure is superior to and safer than open operation. Attention is drawn to the curious fact that the incidence of intussusception is much higher in Britain and Scandinavia than in the United States. There are only six to eight cases a year in Ravitch's clinic, contrasting with 30 to 40 cases a year in any big Children's Hospital in this country.

There is an excellent chapter on errors in diagnosis, leading to delay and even to death of the child. Common mistakes are misdiagnosing intussusception as dysentery, and preoccupation with an associated serious illness. This chapter contains much valuable information.

In the chapter on symptomatology and physical signs, the omission of 'pallor' is a curious one, since it is so common a feature.

There is a section on experimental studies on dogs, in whom intussusception was artificially induced. This proves that the apex of the returning limb of the intussusception is the first to go gangrenous. This also shows that micro-organisms can be found on the serosal surface of the bowel in from four to 48 hours, and the more completely the blood supply is arrested, the more rapidly do they pass through the bowel wall. This underlines the importance of antibiotic therapy.

Resection procedures are discussed. Almost every manoeuvre has been tried at some time. Primary resection and anastomosis is still the treatment of choice and holds the field today, but in the extremely ill baby or with oedematous bowel of doubtful viability, there is a place for a decompressive resection of the Mikulicz type, coupled perhaps with anastomosis. Resections in any single clinic are so few that comparison of results is, in Ravitch's opinion, difficult.

Every clinic has experience of the child who arrives almost irretrievably moribund early in the disease. There is no full discussion in this book of that most important though still mysterious topic, the cause of death in this form of obstruction. There are no hints as to the possible aetiology of intussusception. This, too, remains a mystery.

The production as a whole is excellent, easy to read and profusely illustrated by first-class radiographic studies. There is a very full bibliography.

This book should be read by all those who are called upon to treat intussusception in childhood.

**Kranke Sauglinge.** Edited by C. H. VERBOOM. (Pp. xii + 367; 8 figs. D.M. 39.60.) Stuttgart: George Thieme. 1960.

As its title implies, this book deals with clinical conditions arising in infancy. There are 20 chapters, the lengthiest of which deal with illnesses in the newborn, congenital defects, feeding problems, vitamin deficiencies, infectious diseases and modern therapy. A chapter is devoted to tetany, infections of the cranial contents and acrodynia. Other subjects dealt with include diseases of the respiratory, urinary, haemopoietic and integumentary systems and of the ear, nose, throat and eyes. Emphasis is on treatment, including prophylaxis considered against the background of health in infancy. Intended for the practitioner, the publication is essentially a reference book. It is based upon the combined experience of six clinicians who practise their different specialities at the Infant Clinic of the University of Freiburg i.Br. Sound material is presented in highly concentrated form. Illustrations number only eight and all relate to laboratory aids. There are no references but a selected bibliography is provided. The book is unlikely to appeal on any large scale to paediatricians or general practitioners in this country.

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